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(54) Title: CELULLAR CHOLESTEROL ABSORPTION MODIFIERS

(57) Abstract: The present invention relates to compounds and methods useful as inhibitors of cholesterol absorption for the treatment or prevention of cholesterol-related diseases, such as atherosclerosis.

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CELULLAR CHOLESTEROL ABSORPTION MODIFIERS

FIELD OF THE INVENTION

The present invention is directed to new compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods of modulation of cholesterol absorption activity in a human or animal subject are also provided for the treatment diseases such as vascular disease and atherosclerosis.

BACKGROUND OF THE INVENTION

A factor leading to development of vascular disease, a leading cause of death in industrialized nations, is elevated serum cholesterol. It is estimated that 19% of Americans between the ages of 20 and 74 years of age have high serum cholesterol. The most prevalent form of vascular disease is arteriosclerosis, a condition associated with the thickening and hardening of the arterial wall. Arteriosclerosis of the large vessels is referred to as atherosclerosis. Atherosclerosis is the predominant underlying factor in vascular disorders such as coronary artery disease, aortic aneurysm, arterial disease of the lower extremities and cerebrovascular disease.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol can inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

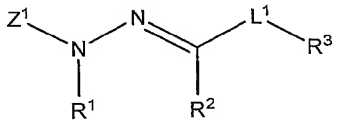
The regulation of whole-body cholesterol homeostasis in mammals and animals involves the regulation of intestinal cholesterol absorption, cellular cholesterol trafficking, dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis, steroid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteins. Regulation of intestinal cholesterol absorption has proven to be an effective means by which to regulate serum cholesterol levels. For example, a cholesterol absorption inhibitor, ezetimibe has been shown to be effective in this regard. Ezetimibe is believed to prevent cholesterol absorption by inhibiting NPC1L1. (US patent 5,846,966 and RE37721). Furthermore, data has been presented that transcription of two cholesterol modifying proteins, HMG COA Synthase and ABCA1 (ATPase binding cassette protein Family A1) are regulated by NPC1L1, see Davis, et al, (2004) JBC 32:,.33586–33592. In this paper, both NPC1L1 knockout animals and normal animals treated with Ezetimibe show decreased expression of HMG COA synthase and increased expression of ABCA1. It should be noted that other cholesterol modifying agents, such as statins, show a similar transcriptional profile in regards to ABCA1; see Wong, et al., (2004) Arteriosclerosis, Thrombosis, and Vascular Biol. 24:2365, suggesting that this is a common compensatory theme in effective cholesterol modifying agents.

NPC1L1 is an N-glycosylated protein comprising a trans-Golgi network to plasma membrane transport signal; (see Bos, et al., (1993) EMBO J. 12:2219-2228; Humphrey, et al., (1993) J. Cell. Biol. 120:1123-1135; Ponnambalam, et al., (1994) J. Cell. Biol. 125:253-268 and Rothman, et al., (1996) Science 272:227-234) which exhibits limited tissue distribution and gastrointestinal abundance. Also, the human *NPC1L1* promoter includes a Sterol Regulated Element Binding Protein 1 (SREBP1) binding consensus sequence (Athanikar, et al., (1998) Proc. Natl. Acad. Sci. USA 95:4935-4940; Ericsson, et al., (1996) Proc. Natl. Acad. Sci. USA 93:945-950; Metherall, et al., (1989) J. Biol. Chem. 264:15634-15641; Smith, et al., (1990) J. Biol. Chem. 265:2306-2310; Bennett, et al., (1999) J. Biol. Chem. 274:13025-13032 and Brown, et al., (1997) Cell 89:331-340). NPC1L1 has 42% amino acid sequence homology to human NPC1 (Genbank Accession No. AF002020), a receptor responsible for Niemann-Pick C1 disease (Carstea, et al., (1997) Science 277:228-231). Niemann-Pick C1 disease is a rare genetic disorder in humans which results in accumulation of low density lipoprotein (LDL)-derived unesterified cholesterol in lysosomes (Pentchev, et al., (1994) Biochim. Biophys. Acta. 1225: 235-243 and Vanier, et al., (1991) Biochim. Biophys. Acta. 1096:328-337). In addition, cholesterol accumulates in the trans-Golgi network of npc1.sup- cells, and relocation of cholesterol, to and from the plasma membrane, is delayed. NPC1 and NPC1L1 each possess 13 transmembrane spanning segments as well as a sterol-sensing domain (SSD). Several other proteins, including HMG-CoA Reductase (HMG-R), Patched (PTC) and Sterol Regulatory Element Binding Protein Cleavage-Activation Protein (SCAP), include an SSD which is involved in sensing cholesterol levels possibly by a mechanism which involves direct cholesterol binding (Gil, et al., (1985) Cell 41:249-258; Kumagai, et al., (1995) J. Biol. Chem. 270:19107-19113 and Hua, et al., (1996) Cell 87:415-426).

SUMMARY OF THE INVENTION

Novel compounds and pharmaceutical compositions that prevent cholesterol absorption by presumably inhibiting NPC1L1, though the mechanism of action of these compounds are still to be confirmed, have been found together with methods of synthesizing and using the compounds including methods for inhibiting or modulating cholesterol absorption in a patient by administering the compounds.

The present invention discloses a class of compounds, useful in treating NPC-1L1-mediated disorders and conditions, defined by structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

Z^1 is selected from the group consisting of Y^1, Y^2, and Y^3;

Y^1 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, perhaloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

Y^2 is selected from the group consisting of R^4–L^2–C(O)– and R^4–L^2–C(S); Y^3 is $C(R^5)(R^6)(R^7)$;

L^1 and L^2 are independently selected from the group consisting of a bond and optionally substituted lower alkyl;

R^1 is selected from the group consisting of hydrogen, lower acyl, lower alkyl; lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^2 is selected from the group consisting of hydrogen, -S-, cyano, formyl, lower acyl, lower alkyl, heteroaryl, and aryl, any of which may be optionally substituted; or R^1 and R^2, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or heteroaryl moiety;

R^3 is selected from the group consisting of lower acyl, lower alkenyl, lower alkenylsulfonyl, lower alkyl, lower alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, heteroaryl, heteroarylsulfonyl, heterocycloalkyl, and heterocycloalkylsulfonyl, any of which may be optionally substituted; or R^2 and R^3, together with the atoms to which they are attached, may be joined to form an optionally substituted cycloalkyl or heterocycloalkyl moiety;

R^4 is selected from the group consisting of hydrogen, aryl, arylalkoxy, arylalkylamino, arylalkylthio, arylamino, aryloxy, arylthio, heteroarylalkoxy, heteroarylalkylamino, heteroarylalkylthio, heteroaryl, heteroarylthio, heterocycloalkyl, and heterocycloalkylthio, any of which may be optionally substituted; or R^2 and R^4, taken together with the atoms to which they are attached, may form an optionally substituted heteroaryl or optionally substituted heterocycloalkyl moiety; and

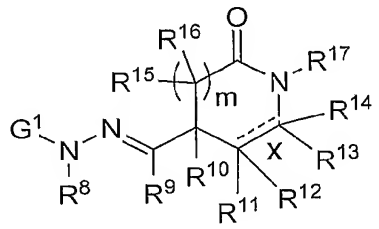
R^5, R^6, and R^7 are independently selected from the group consisting of hydrogen, -S-, amido, aryl, lower alkyl, and heteroaryl, any of which may be optionally substituted.

Compounds according to the present invention possess useful NPC-1L1 inhibiting or cholesterol absorption-inhibiting activity, and may be used in the treatment or prophylaxis of a disease or condition in which cholesterol absorption plays an active role. Thus, in broad aspect, the present invention also provides pharmaceutical compositions comprising one or more compounds of the present invention together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. In certain embodiments, the present invention provides methods for preventing cholesterol absorption by presumably inhibiting NPC1L1. In other embodiments, the present invention provides methods for treating a cholesterol absorption -mediated disorder in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. The present invention also contemplates

the use of compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the modulation of cholesterol absorption or by inhibiting NPC1L1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention further discloses a class of compounds, useful in treating NPC-1L1-mediated disorders and conditions, defined by structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

G^1 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, perhaloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^8 is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^9 is selected from the group consisting of hydrogen, cyano, formyl, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower perhaloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^8 and R^9, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, and lower alkynyl, any of which may be optionally substituted; or R^9 and R^{10}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{11} and R^{14} are independently selected from the group consisting of hydrogen, cyano, lower alkyl, lower alkenyl, lower alkynyl, and lower cycloalkyl, any of which may be optionally substituted; or R^{11} and R^{14}, together with the atoms to which they are attached, may be joined to form an aryl, heteroaryl, heterocycloalkyl or cycloalkyl moiety, any of which may be optionally substituted;

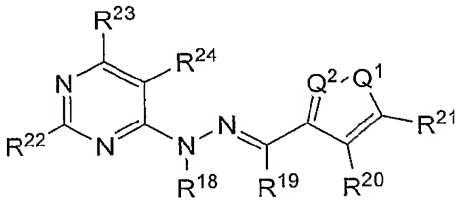
R^{12} and R^{13} are independently selected from the group consisting of null, hydrogen or optionally substituted lower alkyl;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl; or R^{16} and R^{16}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

m is an integer from 0 to 3; and

R^{17} is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower aminoalkyl, lower cycloalkyl, lower cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{14} and R^{17}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl moiety.

The present invention further discloses a class of compounds, useful in treating NPC-1L1-mediated disorders and conditions, defined by structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^{18} is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower perhaloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{20}, R^{21}, R^{23} and R^{24} are independently selected from the group consisting of hydrogen, amino, hydroxy, carbamoyl, carboxy, halogen, cyano, nitro, lower acyl, lower acylamino, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkylthioalkyl, lower alkenyl, lower alkynyl, lower aminoalkyl, lower aminocarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylalkynyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, lower haloalkoxy, lower haloalkyl, lower perhaloalkyl, lower heteroalkyl, lower perhaloalkoxy, trihalomethanesulfonamido, trihalomethanesulfonyl, trihalomethoxy, trisubstituted silyl,

heterocycloalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, any of which may be optionally substituted; or R^{20} and R^{21}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted; or R^{23} and R^{24}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted;

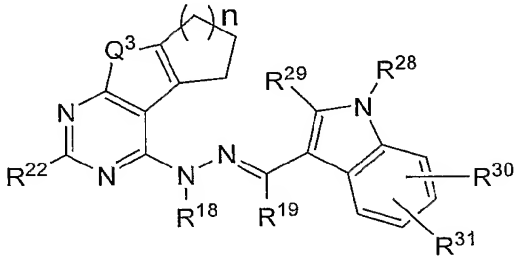
R^{22} is selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, lower haloalkoxy, lower perhaloalkyl, lower perhaloalkoxy, and trihalomethoxy;

Q^1 is selected from the group consisting of $N(R^{25})$, O, and S;

Q^2 is selected from the group consisting of $N(R^{26})$, $C(R^{27})$, O, and S; and

R^{25}, R^{26} and R^{27} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, and lower perhaloalkyl.

The present invention further discloses a class of compounds, useful in treating NPC-1L1-mediated disorders and conditions, defined by structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^{18} is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower perhaloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{22} is selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, lower haloalkoxy, lower perhaloalkyl, lower perhaloalkoxy, and trihalomethoxy;

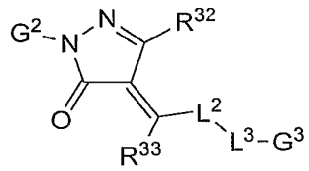
Q^3 is selected from the group consisting of $N(R^{28})$, O, and S;

n is an integer from 1 to 4;

$R^{28}$and R^{29} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, and lower perhaloalkyl; and

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, amino, hydroxy, carbamoyl, carboxy, halogen, cyano, nitro, lower acyl, lower acylamino, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkylthioalkyl, lower alkenyl, lower alkynyl, lower aminoalkyl, lower aminocarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylalkynyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, lower haloalkoxy, lower haloalkyl, lower perhaloalkyl, lower heteroalkyl, lower perhaloalkoxy, trihalomethanesulfonamido, trihalomethanesulfonyl, trihalomethoxy, trisubstituted silyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, any of which may be optionally substituted.

The present invention further discloses a class of compounds, useful in treating NPC-1L1-mediated disorders and conditions, defined by structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

G^2 and G^3 are independently selected from the group consisting of aryl, lower cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may be optionally substituted;

R^{32} is selected from the group consisting of hydrogen, carbamoyl, cyano, lower acyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, lower aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, carboxy, lower perhaloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl, any of which may be optionally substituted;

R^{33} is selected from the group consisting of hydrogen, lower acyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkenyl, lower alkynyl, lower aminocarbonylalkyl, lower perhaloalkyl, any of which may be optionally substituted;

L^2 is selected from the group consisting of $N(R^{34})$, O, and S;

L^3 is selected from the group consisting of a bond, -NHC(=O)-, -C(R^{35}) (R^{36})-; and

R^{34}, R^{35} and R^{36} are independently selected from the group consisting of hydrogen and optionally substituted alkyl.

In certain embodiments, the compounds of the present invention have structural Formula I, wherein:

Y^1 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

Y^2 is R^4–L^2–C(O)– ;

R^1 is selected from the group consisting of hydrogen and optionally substituted alkyl;

R^2 is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted heteroaryl, and optionally substituted aryl;

R^3 is selected from the group consisting of lower acyl, aryl, arylsulfonyl, heteroaryl, heteroarylsulfonyl, heterocycloalkyl, and heterocycloalkylsulfonyl, any of which may be optionally substituted; and

R^4 is selected from the group consisting of aryl, arylalkoxy, arylalkylamino, arylamino, aryloxy, arylthio, heteroarylalkoxy, heteroaryl, and heteroarylthio, any of which may be optionally substituted; or R^2 and R^4, taken together with the atoms to which they are attached, may form an optionally substituted heteroaryl or optionally substituted heterocycloalkyl moiety.

In other embodiments, the compounds of the present invention have structural Formula I, wherein:

Z^1 is Y^1;

L^1 is a bond;

R^1 is optionally substituted alkyl;

R^2 is hydrogen and optionally substituted lower alkyl; and

R^3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

In certain embodiments, the compounds of the present invention have structural Formula II, wherein:

G^1 is selected from optionally substituted aryl and optionally substituted heteroaryl;

R^8 is selected from the group consisting of hydrogen, lower alkyl, aryl and heteroaryl, any of which may be optionally substituted;

R^9 is selected from the group consisting of hydrogen, cyano, formyl, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted; or R^8 and R^9, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{10} is selected from the group consisting of hydrogen and optionally substituted lower alkyl; or R^9 and R^{10}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{11} and R^{14} are independently selected from the group consisting of hydrogen, cyano, and optionally substituted lower alkyl; or R^{11} and R^{14}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

m is an integer from 1 to 2; and

R^{17} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; or R^{14} and R^{17}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted heterocycloalkyl moiety.

In some embodiments, the compounds of the present invention have structural Formula II, wherein:

G^1 is optionally substituted heteroaryl;

R^8 is optionally substituted lower alkyl;

R^9 is hydrogen;

R^{10} is hydrogen;

R^{11} and R^{14} are independently selected from the groups consisting of cyano or optionally substituted lower alkyl;

R^{12} and $R^{13}$are null;

R^{15} and R^{16} are hydrogen;

m is 1; and

R^{17} is hydrogen.

In certain embodiments, the compounds of the present invention have structural Formula III, wherein:

R^{18} is selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{20}, R^{21}, R^{23} and R^{24} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl,

lower alkylthio, aryl, arylalkyl, lower perhaloalkyl, lower perhaloalkoxy, heterocycloalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; or R^{20} and R^{21}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted; or R^{23} and R^{24}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted;

R^{22} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

Q^1 is selected from the group consisting of $N(R^{25})$, O, and S;

Q^2 is $C(R^{27})$; and

R^{25} and R^{27} are independently selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl.

In other embodiments, the compounds of the present invention have structural Formula III, wherein:

R^{18} is selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R^{19} is selected from the group consisting of hydrogen and optionally substituted alkyl; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{20} and R^{21}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted; or R^{23} and R^{24}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted; and

R^{22} is selected from the group consisting of hydrogen and optionally substituted lower alkyl.

In further certain embodiments, the compounds of the present invention have structural Formula IV, wherein:

R^{18} is selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{22} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

R^{28} and R^{29} are independently selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, and lower alkylsulfonyl; and

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower perhaloalkyl, and lower perhaloalkoxy, any of which may be optionally substituted.

In yet other embodiments, the compounds of the present invention have structural Formula IV, wherein:

R^{18} is selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R^{19} is selected from the group consisting of hydrogen and optionally substituted alkyl;

R^{22} is selected from the group consisting of hydrogen and optionally substituted lower alkyl;

Q^3 is S;

n is the integer 2; and

R^{28} and R^{29} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R^{30} and R^{31} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl.

In certain embodiments, the compounds of the present invention have structural Formula V, wherein:

G^2 and G^3 are independently selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted';

R^{32} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

R^{33} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

L^2 is $N(R^{34})$; and

R^{34}, R^{35} and R^{36} are hydrogen.

In still further embodiments, the compounds of the present invention have structural Formula V, wherein:

G^2 and G^3 are independently selected from optionally substituted aryl;

R^{32} is optionally substituted lower alkyl;

L^3 is a bond; and

R^{33} is hydrogen.

In another embodiment, the invention provides for compounds selected from the Examples 1-51, as shown in Table 1.

As used herein, the terms below have the meanings indicated.

The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. Examples of acyl groups include formyl, alkanoyl and aroyl radicals.

The term "acylamino" embraces an amino radical substituted with an acyl group. An example of an "acylamino" radical is acetylamino ($CH_3C(O)NH-$).

The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20, preferably 2 to 6, carbon atoms. Alkenylene refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl radicals include ethenyl, 1-propenyl, 2-propenyl (allyl), 2-methyl-1-propenyl, 2-methyl-2-propenyl (methylallyl), 3-methyl-2-butenyl (prenyl), 1,4-butadienyl and the like.

The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

The term "alkoxyalkoxy," as used herein, alone or in combination, refers to one or more alkoxy groups attached to the parent molecular moiety through another alkoxy group. Examples include ethoxyethoxy, methoxypropoxyethoxy, ethoxypentoxyethoxyethoxy and the like.

The term "alkoxyalkyl," as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through an alkyl group. The term "alkoxyalkyl" also embraces alkoxyalkyl groups having one or more alkoxy groups attached to the alkyl group, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups.

The term "alkoxycarbonyl," as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group. Examples of such "alkoxycarbonyl" groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl.

The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to and including 20, preferably 1 to 10, and more preferably 1 to 6, carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($-CH_2-$).

The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "alkylaminocarbonyl" as used herein, alone or in combination, refers to an alkylamino group attached to the parent molecular moiety through a carbonyl group. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl.

The term "alkylcarbonyl" and "alkanoyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl.

The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

The term "alkylsulfinyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfinyl group. Examples of alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term "alkylsulfonyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group. Examples of alkylsulfinyl groups include methanesulfonyl, ethanesulfonyl, tert-butanesulfonyl, and the like.

The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, ethoxyethylthio, methoxypropoxyethylthio, ethoxypentoxyethoxyethylthio and the like.

The term "alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. Alkylthioalkyl radicals include "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl.

The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20, preferably from 2 to 6, more preferably from 2 to 4, carbon atoms. "Alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl, and the like.

The term "amido," as used herein, alone or in combination, refers to an amino group as described below attached to the parent molecular moiety through a carbonyl group. The term "C-amido" as used herein, alone or in combination, refers to a -C(=O)-NR_2 group with R as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(=O)NH- group, with R as defined herein.

The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, and heterocycloalkyl, wherein the aryl, the aryl part of the arylalkenyl, the arylalkyl, the heteroaryl, the heteroaryl part of the heteroarylalkenyl and the heteroarylalkyl, the heterocycle, and the heterocycle part of the heterocycloalkenyl and the heterocycloalkyl can be optionally substituted as defined herein with one, two, three, four, or five substituents.

The term "aminoalkyl," as used herein, alone or in combination, refers to an amino group attached to the parent molecular moiety through an alkyl group. Examples include aminomethyl, aminoethyl and aminobutyl.

The terms "aminocarbonyl" and "carbamoyl," as used herein, alone or in combination, refer to an amino-substituted carbonyl group, wherein the amino group can be a primary or secondary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aminocarbonylalkyl," as used herein, alone or in combination, refers to an aminocarbonyl radical attached to an alkyl radical, as described above. An example of such radicals is aminocarbonylmethyl. The term "amidino" denotes an $-C(NH)NH_2$ radical. The term "cyanoamidino" denotes an $-C(N-CN)NH_2$ radical.

The term "aralkenyl" or "arylalkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

The term "aralkoxy" or "arylalkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "aralkyl" or "arylalkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

The term "aralkylamino" or "arylalkylamino," as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a nitrogen atom, wherein the nitrogen atom is substituted with hydrogen.

The term "aralkylidene" or "arylalkylidene," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkylidene group

The term "aralkylthio" or "arylalkylthio," as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a sulfur atom.

The term "aralkynyl" or "arylalkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

The term "aralkoxycarbonyl," as used herein, alone or in combination, refers to a radical of the formula aralkyl-O–C(O)– in which the term "aralkyl," has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl (Z or Cbz) and 4-methoxyphenylmethoxycarbonyl (MOS).

The term "aralkanoyl," as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like. The term "aroyl" refers to an acyl radical derived from an arylcarboxylic acid, "aryl" having the meaning given below. Examples of such aroyl radicals include substituted and unsubstituted benzoyl or napthoyl such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2-naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as benzyl, phenyl, naphthyl, anthracenyl, phenanthryl, indanyl, indenyl, annulenyl, azulenyl, tetrahydronaphthyl, and biphenyl.

The term "arylamino" as used herein, alone or in combination, refers to an aryl group attached to the parent moiety through an amino group, such as methylamino, N-phenylamino, and the like.

The terms "arylcarbonyl" and "aroyl," as used herein, alone or in combination, refer to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "arylsulfonyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "arylthio," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfur atom.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$.

The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent radical $C_6H_4=$ derived from benzene. Examples include benzothiophene and benzimidazole.

The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NR, group-with R as defined herein.

The term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NH- group, with R as defined herein.

The term "carbonyl," as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

The term "carboxy," as used herein, refers to –C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O– group, where R is as defined herein. A "C-carboxy" group refers to a –C(O)OR groups where R is as defined herein.

The term "cyano," as used herein, alone or in combination, refers to –CN.

The term "cycloalkyl," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 12, preferably five to seven, carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydonapthalene, octahydronapthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by bicyclo[2,2,2]octane, bicyclo[2,2,2]octane, bicyclo[1,1,1]pentane, camphor and bicyclo[3,2,1]octane.

The term "ester," as used herein, alone or in combination, refers to a carbonyl group bridging two moieties linked at carbon atoms.

The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a halohydrocarbyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($–CF_2–$), chloromethylene (–CHCl–) and the like. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, perfluorodecyl and the like.

The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, -CH2-NH-OCH3.

The term "heteroaryl," as used herein, alone or in combination, refers to 3 to 7 membered, preferably 5 to 7 membered, unsaturated heterocyclic rings wherein at least one atom is selected from

the group consisting of O, S, and N. Heteroaryl groups are exemplified by: unsaturated 3 to 7 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.]tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.]etc.; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.]and isothiazolyl; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.]and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuryl, benzothienyl, and the like.

The term "heteroaralkenyl" or "heteroarylalkenyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkenyl group.

The term "heteroaralkoxy" or "heteroarylalkoxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkoxy group.

The term "heteroarylalkyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkyl group.

The term "heteroaralkylidene" or "heteroarylalkylidene," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkylidene group.

The term "heteroaryloxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an oxygen atom.

The term "heteroarylsulfonyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through a sulfonyl group.

The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic radical containing at least one, preferably 1 to 4, and more preferably 1 to 2 heteroatoms as ring members, wherein each said heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein there are preferably 3 to 8 ring members in each ring, more preferably 3 to 7 ring members in each ring, and most preferably 5 to 6 ring members in

each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Heterocycle groups of the invention are exemplified by aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

The term "heterocycloalkenyl," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkenyl group.

The term "heterocycloalkoxy," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular group through an oxygen atom.

The term "heterocycloalkyl," as used herein, alone or in combination, refers to an alkyl radical as defined above in which at least one hydrogen atom is replaced by a heterocyclo radical as defined above, such as pyrrolidinylmethyl, tetrahydrothienylmethyl, pyridylmethyl and the like.

The term "heterocycloalkylidene," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkylidene group.

The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., –N–N–.

The term "hydroxy," as used herein, alone or in combination, refers to –OH.

The term "hydroxyalkyl" as used herein, alone or in combination, refers to a linear or branched alkyl group having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

The term "imino," as used herein, alone or in combination, refers to =N–.

The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N–O–.

The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of this invention.

The term "isocyanato" refers to a –NCO group.

The term "isothiocyanato" refers to a –NCS group.

The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

The term "lower," as used herein, alone or in combination, means containing from 1 to and including 6 carbon atoms.

The term "mercaptoalkyl" as used herein, alone or in combination, refers to an R'SR– group, where R and R' are as defined herein.

The term "mercaptomercaptyl" as used herein, alone or in combination, refers to a RSR'S– group, where R is as defined herein.

The term "mercaptyl" as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.

The term "null" refers to the absence of a substituent or group..

The term "nitro," as used herein, alone or in combination, refers to $–NO_2$.

The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

The term "oxo," as used herein, alone or in combination, refers to =O.

The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

The term "sulfonyl," as used herein, alone or in combination, refers to $–SO_2–$.

The term "N-sulfonamido" refers to a $RS(=O)_2NH$- group with R as defined herein.

The term "S-sulfonamido" refers to a $-S(=O)_2NR_2$, group, with R as defined herein.

The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

The term "thioether," as used herein, alone or in combination, refers to a thio group bridging two moieties linked at carbon atoms.

The term "thiol," as used herein, alone or in combination, refers to an –SH group.

The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

The term "N-thiocarbamyl" refers to an ROC(S)NH– group, with R as defined herein.

The term "O-thiocarbamyl" refers to a –OC(S)NR, group with R as defined herein.

The term "thiocyanato" refers to a –CNS group.

The term "trihalomethanesulfonamido" refers to a $X_3CS(O)_2NR–$ group with X is a halogen and R as defined herein.

The term "trihalomethanesulfonyl" refers to a $X_3CS(O)_2–$ group where X is a halogen.

The term "trihalomethoxy" refers to a $X_3CO–$ group where X is a halogen.

The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethylsilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, thiol, lower alkylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylsulfinyl, arylsulfonyl, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, CO_2CH_3, $C(O)NH_2$, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., -CH2CH_3), fully substituted (e.g., -CF_2CF_3), monosubstituted (e.g., -CH_2CH_2F) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., -CH_2CF_3). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R" where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence.

The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified.

The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each

active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

"Cholesterol absorption inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to downregulation of ABCA1 transcription while upregulating the expression of HMG COA synthase activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the luciferase reporter HEP ABCA1 Luc assay described generally hereinbelow. "IC_{50}" is that concentration of inhibitor which reduces the level of ABCA1 expression to half-maximal level while increasing expression of HMG COA synthase. Representative compounds of the present invention have been discovered to exhibit inhibitory activity against cholesterol absorption, presumably by inhibiting NPC1L1. Compounds of the present invention preferably exhibit an IC_{50} with respect to downregulation of ABCA1 transcription while upregulating the expression of HMG COA synthase activity of no more than about 10 μM, more preferably, no more than about 5 μM, even more preferably not more than about 1 μM, and most preferably, not more than about 200 nM, as measured in luciferase reporter HEP ABCA1 Luc assay described herein.

The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

The term "prodrug" refers to a compound that is made more active in vivo. The present compounds can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for

use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible; which are suitable for treatment of diseases without undue toxicity, irritation, and allergic-response; which are commensurate with a reasonable benefit/risk ratio; and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds of the compounds of the present invention and the like.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

The compounds of the present invention can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may

be of utility in the preparation and purification of the compound in question. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, the subject invention provides a pharmaceutical formulation comprising a compound or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may

optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Compounds of the present invention may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The compounds of the subject invention can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

Specific, non-limiting examples of possible combination therapies include use of a compound of the present invention as defined above or a pharmaceutically acceptable salt thereof; and at least one active ingredient selected from:

a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-IB (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors such as DPP728, LAF237 (vildagliptin - Example 1 of WO 00/34241), MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidinedione derivative (glitazone) such as pioglitazone, rosiglitazone, or (*R*)-1-{4-[5-methyl-2-(4-

trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}2,3-dihydro-1*H*-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, a non-glitazone type PPARδ agonist e.g. GI-262570;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) an anti-obesity agent or appetite regulating agent such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine or cannabinoid receptor antagonists;

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutral endopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin n antagonists such as candesartan, eprosartan, irbesartan, losartan, tehnisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

e) a HDL increasing compound;

f) Cholesterol absorption modulator such as Zetia® and KT6-971;

g) Apo-Al analogues and mimetics;

h) thrombin inhibitors such as Ximelagatran;

i) aldosterone inhibitors such as anastrazole, fadrazole, epierenone;

j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably miatinib ({ N-{5-[4-(4-methyl-piperazino-

methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine}) described in the European patent application EPA-0564409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-l-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and

m) an agent interacting with a 5-HT3 receptor and/or an agent interacting with 5-HT4 receptor such as tegaserod described in the US patent No. 5510353 as example 13, tegaserod hydrogen maleate, cisapride, cilansetron;

or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

Most preferred combination partners are cholesterol absorption modulator such as Zetia® and KT6-971or hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin.

In any case, the multiple therapeutic agents (at least one of which is a compound of the present invention) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

Thus, in another aspect, the present invention provides methods for treating NPC-1L1-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of the present invention effective to reduce or prevent said disorder in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, the present invention provides therapeutic compositions comprising at least one compound of the present invention in combination with one or more additional agents for the treatment of NPC-1L1-mediated disorders.

The present invention includes compounds listed above in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question.

Thus, preferred salts include hydrochloride, hydrobromide, sulfonate, citrate, tartrate, phosphonate, lactate, pyruvate, acetate, succinate, oxalate, fumarate, malate, oxaloacetate, methanesulfonate, ethanesulfonate, p-toluenesulfonate, benzenesulfonate and isethionate salts of compounds of the present invention. A salt of a compound can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

Asymmetric centers exist in the compounds of the present invention. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

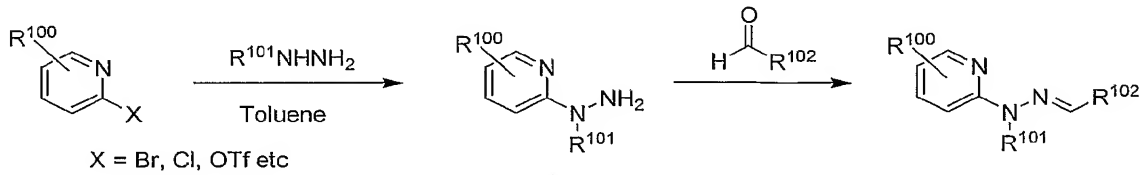
Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

All references, patents or applications, U.S. or foreign, cited herein are hereby incorporated by reference as if written herein in their entirety.

GENERAL SYNTHETIC METHODS FOR PREPARING COMPOUNDS

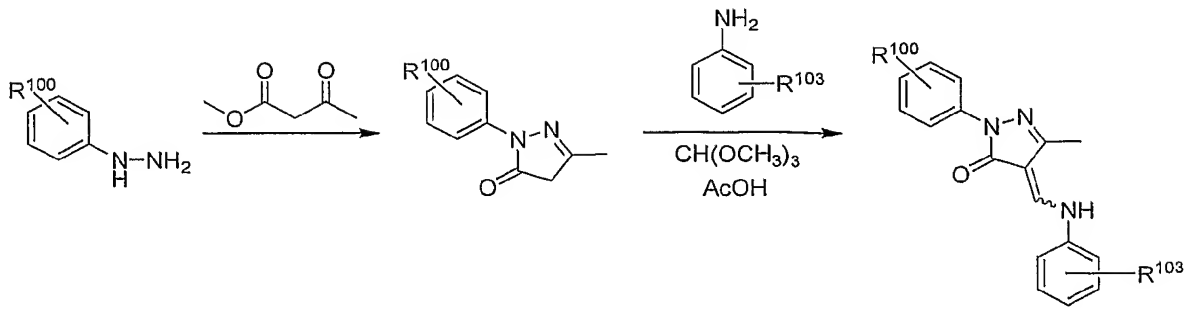
Examples 1- 52 can generally be synthesized using the following general synthetic procedures set forth below.

Scheme I



X = Br, Cl, OTf etc

R^{101} = H, Me



The activity of the compounds in Examples 1-52 as cholesterol-absorption inhibitors and presumably, though the authors do not wish to be held to this theory, NPC1L1 inhibitors, is illustrated in the following assays. The other compounds listed below, which have not yet been made and/or tested, are predicted to have activity in these assays as well.

Biological Activity Assays

Hepatocyte (HEPG2C3A) Luciferase Reporter Assay

The compounds of the invention have an effect on ABCA-1 gene expression. It is reported that compounds that effect cholesterol production and absorption such as statins and ezetimibe cause a decrease expression of ABCA1 transcript. For example, in NPC1L1 knockout animals (the target of Ezetimibe) and also in wild type animals treated with ezetimibe, a decrease in ABCA1 transcript is seen. Therefore, a stable cell line with 2KB of the ABCA-1 5' promoter region fused to a luciferase reporter was used in a reporter assay to interrogate compounds for the ability to decrease ABCA-1 expression. The promoter region was made by using PCR to obtain the fragment from human genomic DNA using the following primers; sense strand primer: ATAAGTTGGAGGTCTGGGAGTGGCTA and antisense strand primer : GCTCTGTTGGTG-CGCGGAGCT. The genomic fragment included approx 2KB of the genomic ABCA1 (accession number GI:21536375) including promoter elements important to the transcriptional regulation of this gene. To perform the luciferase assays, a human hepatocyte cell line (HEPG2C3A ATCC#CRL-1074; ATCC, Manassas, VA) was stably transfected with the above described fragment cloned into a luciferase containing pGL3 vector. Transient transfections were done initially to insure activity in cells when stimulated with an RXR agonist, 9-cis retinoic acid. Stable cells were made using lentiviral clone construction of the above described ABCA1 clone in a Lentiviral luciferase tagged vector with puromycin selection. Following viral production in 293T cells, HEPG2 C3A cells were infected and put under puromycin selective pressure until cells began to divide and behave normally in the presence of puromycin. As these cells were to be used for an assay to find inhibitors of cholesterol absorption, the presence of NPC1L1 transcript was deemed a necessity (NPC1L1 is a protein shown previously to be important in cholesterol absorption: see patent WO05015988A1). RTPCR was used to determine the presence of NPC1L1 transcript (NM 13389) in

this cell line before and after stable transfection using the following primers: Forward primer ATAGGCGCGCCATGGCGGAGGCCGGCCTGAG and Reverse primer TATGGCGCGCCTCAGAACTGCCGCCCATTGT). RTPCR was performed using Trizol Reagent according to manufacturer's instructions (Invitrogen Corp, Carlsbad Ca) to extract total RNA from the HEPG2C3A cells. The mRNA from these total RNA preparations was amplified using Superscript II reverse transcriptase according to manufacturer's instructions (Invitrogen Corp, Carlsbad Ca) with the oligo dT primer and the random hexamer primer for first strand synthesis provided in the kit. Various primer sets, including those described above were used to confirm the presence of NPC1L1 transcript. The resulting cDNA of NPC1L1 was cloned into an appropriate prokaryotic vector and sequenced to confirm identity. HepG2C3A cells were found to have ample amounts of the NPC1L1 transcript before and after stable transfection. Following confirmation of the presence of NPC1L1, stably transfected cells were expanded for luciferase reporter assays under the selection of puromycin and assayed for luciferase activity following 9-cis retinoic acid stimulation. Luciferase reporter assays were run in high throughput 1536 well format using 5 µl of cells at a concentration of 500000 cells/ml of media. Briefly, cells were plated in MEM media (Invitrogen, Carlsbad, California) supplemented with 1% fetal bovine serum (Invitrogen) for 6 hr in white opaque tissue culture treated Greiner 1536 well plates (USA Scientific, Inc; Ocala, FLA) to promote attachment. Plated cells were then incubated with compound for 12 hr and stimulated with 600nM 9-cis retinoic acid (RA) (Sigma, St Louis MO) following the 12 hr incubation with compound. Cells stimulated with 9-cis RA were incubated for 20 h and then Britelite (PerkinElmer Life And Analytical Sciences, Inc; Boston, MA) was added to determine the total amount of luciferase production as driven by the ABCA1 promoter region described herein. Compounds were profiled in the same cell based assay in duplicate assays in five point dose response format to determine confirmation. To determine potential toxicity of compounds and to insure against "false positives" ATPlite was used in place of Britelite (both products of Perkin Elmer) under the same assay conditions described above. Compounds were chosen on the basis of non-toxic activity and reproducibility of results.

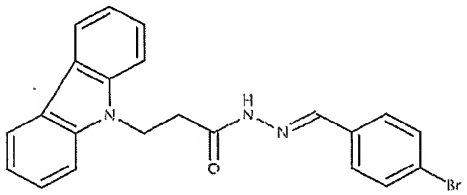
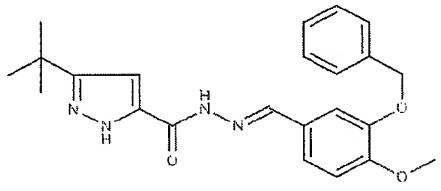
Quantitative Gene Expression Profiling from Cell Lysates by Branched DNA

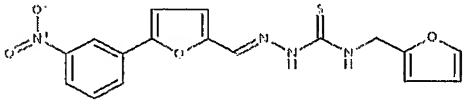
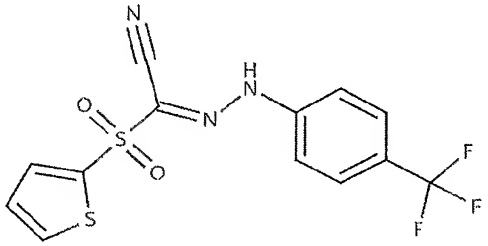
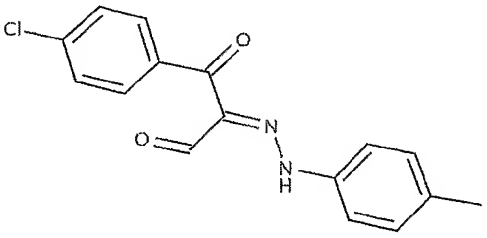
The compounds of the invention modify HMG CoA synthase expression and ABCA1 expression. Branched DNA (bDNA) is a method of accurate RNA quantification that offers RNA quantification directly from cell lysate. The branched DNA technology introduces multiple labels onto a target nucleic acid. The sensitivity stems from the use of a set of branched reporter probes. Each probe has 15 branches, and each branch can react with up to three alkaline phosphatase-labeled detection probes. This leads to a high degree of labeling of the target and kits to perform branched DNA assays can be obtained from Genospectra, Inc (Fremont, CA). Branched DNA assays were performed with select compounds using specific probes for HMG COA synthase and ABCA1 RNA. The HEPG2C3A cells described previously along with the human intestinal cell lines: CaCo2 (ATCC # HTB-237;

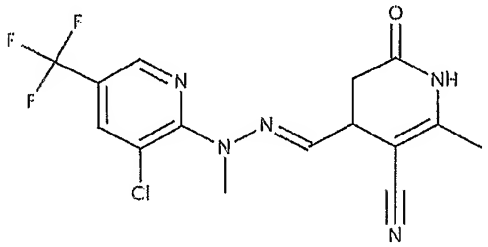
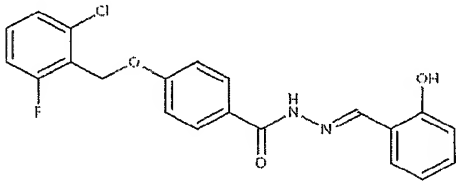
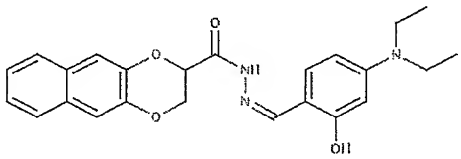
colorectal adenocarcinoma; ATCC: Manassas, VA) and the human intestinal cell line FHs (ATCC # CCL-241; normal fetal small intestine, ATCC: Manassas, VA) were plated in clear bottom 96 well format in 1% fetal bovine serum overnight and treated with compounds the following morning. Cells were plated at a concentration of 200000 cells/ ml media. DMSO (vehicle used for compound dilution) concentration of compounds was kept at 0.8%. Compound remained on cells for 20 hr and cells were lysed following compound incubation according to kit instructions. Lysed cells release mRNA in the presence of target probes. Target mRNA from lysed cells is captured by hybridization and transferred to the Genospectra Capture Plate. Signal amplification is performed by hybridization of the bDNA Amplifier and Label Probe. Addition of chemiluminescence substrate yields a signal that is proportional to the amount of mRNA present in the sample. The target probes used in this experiment were specific to HMG CoA synthase and ABCA1 (NM_005502, cat #PA-10181) purchased from Genospectra and used according to kit instructions. Differential expression as seen with bDNA was qualitatively confirmed with immunofluorescence. Data is represented as (+ or -) for both ABCA1 and HGMG CoA synthase, although to be positive in ABCA1 assay required a minimal 2X decrease in overall transcriptional activity over vehicle control (DMSO) and to be positive in HMG coA synthase required a minimal 2X increase in transcriptional activity of the target gene over DMSO control. Compounds not tested in these assays are designated by "NT". Ezetimibe was used as positive control in bDNA assays as well as antibody experiments. The EC50 of ezetimibe in these assays was calculated to be less than 100nM with an R^2 value of 0.89. Several of compounds tested here show similar EC50s. Briefly, cells were plated and treated with compound as described above and fixed with formaldehyde after compound incubation. Qualitative visualization of protein changes were made (data not shown) using antibodies to HMG CoA synthase protein (chicken polyclonal #AB 14302; Abcam Inc, Cambridge, MA) and ABCA1 protein (mouse monoclonal #AB18180; Abcam Inc, Cambridge, MA) and observing cells microscopically after fluorescent labeling. Qualitative antibody labeling corresponded well with quantitative bDNA results. Ezetimibe (1uM final concentration) was used as positive control in antibody experiments and showed a diminished signal with ABCA1 antibody in Hep G2C3A and CaCo2 cells and was completely absent by antibody staining in FhS cells when compared to DMSO treated cells. The ezetimibe treated cells showed a moderate increase in staining with the HMG CoA synthase antibody when compared to DMSO treated controls.

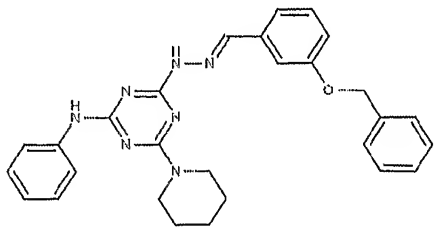
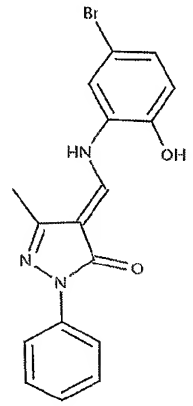
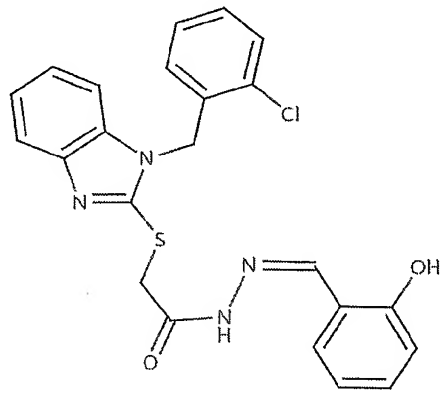
The invention is further illustrated by the following examples and assay data.

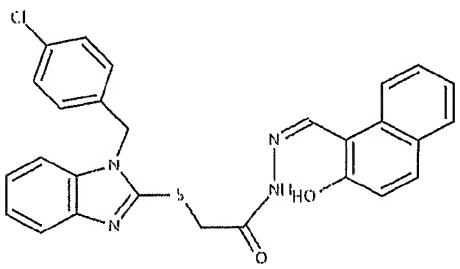
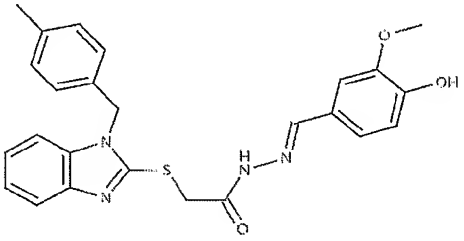
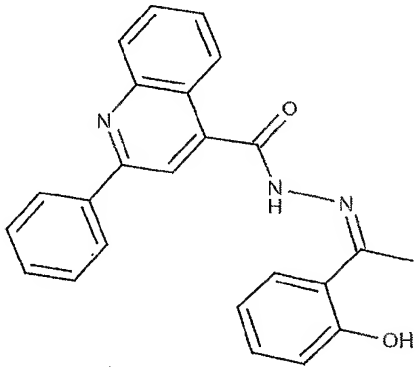
Table 1.

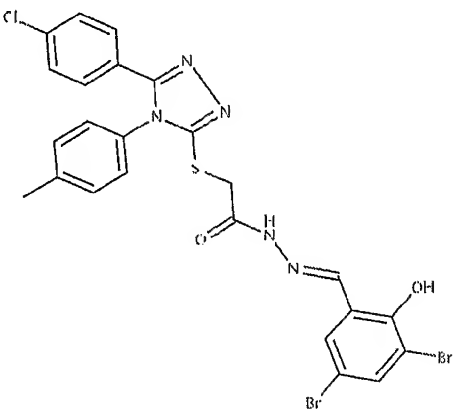
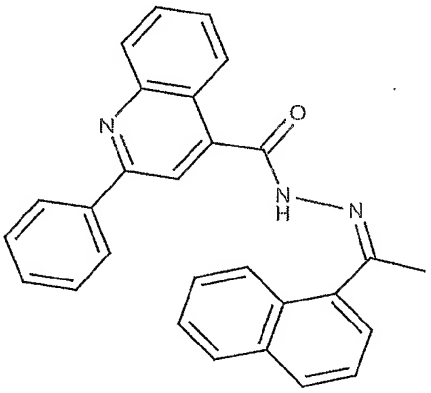
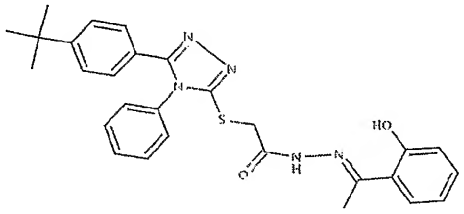
Example	Structure	HEP ABCA1 LUC Reporter Assay	ABCA1 bDNA	HMG CoA Synthase bDNA
1		+	NT	NT
2		–	NT	NT

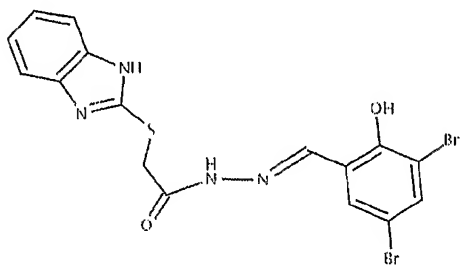
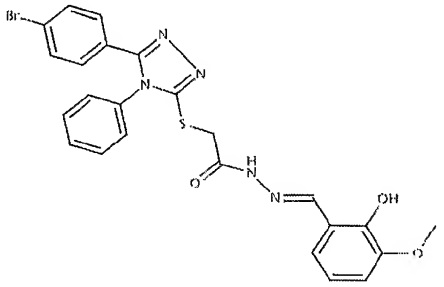
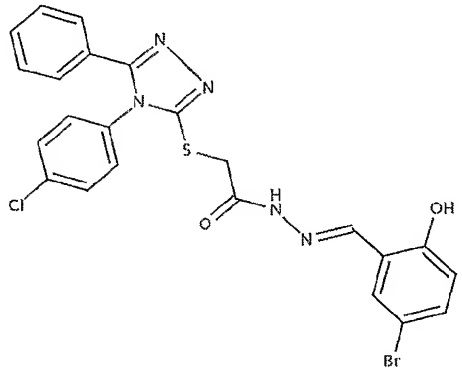
3		+	+	+
4		+	NT	NT
5		+	NT	NT

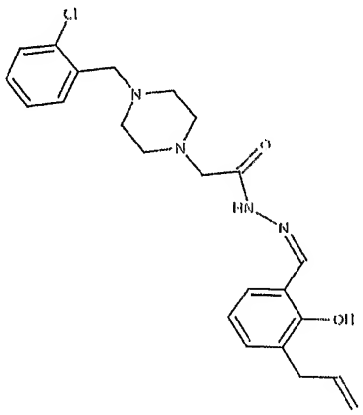
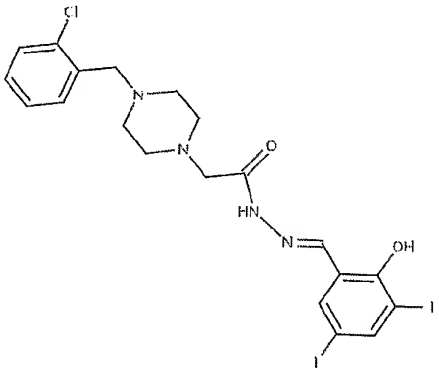
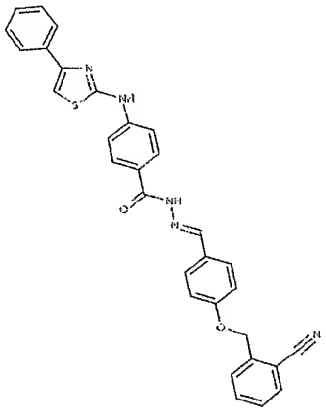
6		+	+	+
7		+	NT	NT
8		+	NT	NT

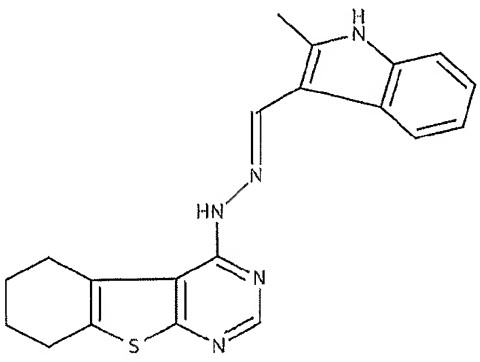
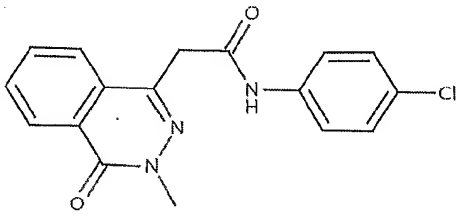
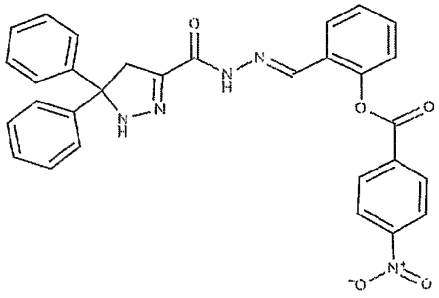
9		+	NT	NT
10		+	+	+
11		+	–	–

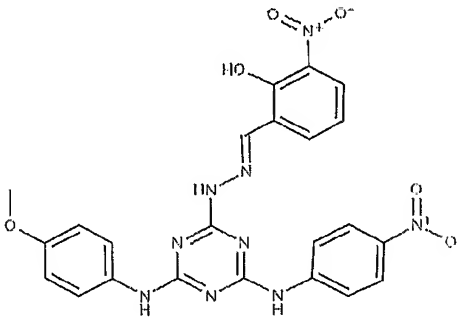
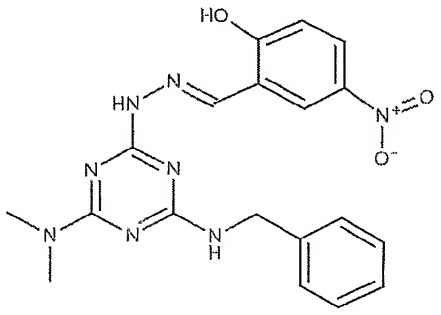
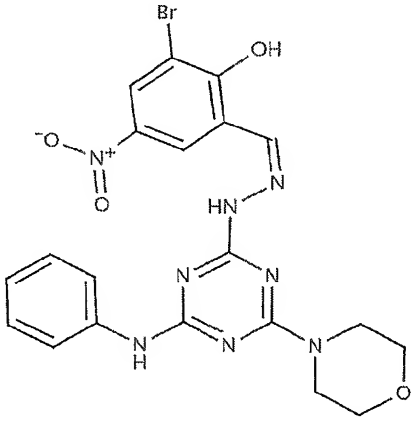
12		+	NT	NT
13		+	–	–
14		+	NT	NT

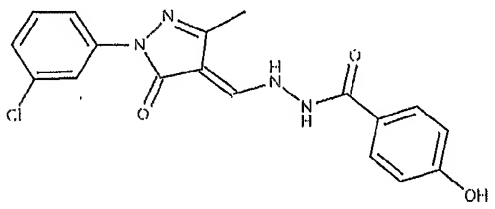
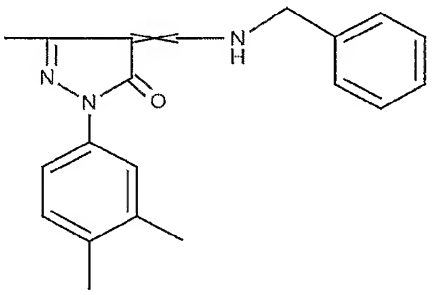
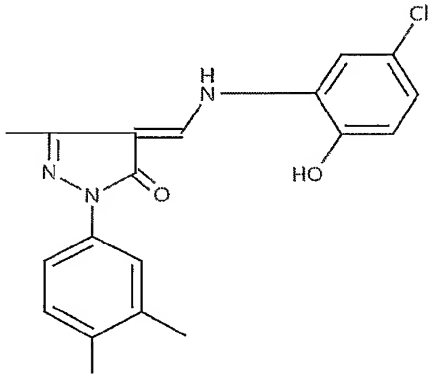
15		+	NT	NT
16		+	NT	NT
17		–	NT	NT

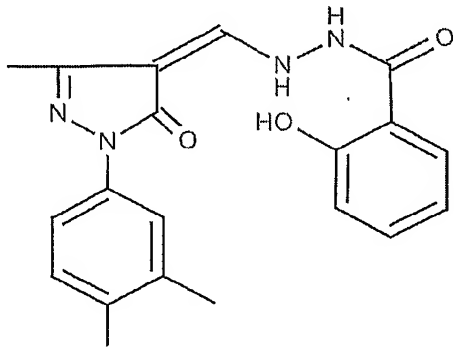
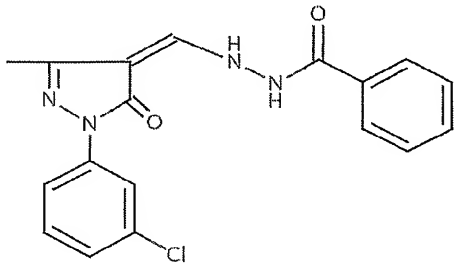
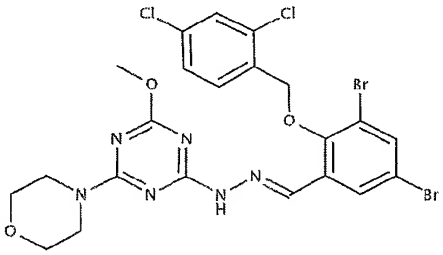
18		+	NT	NT
19		+	NT	NT
20		+	NT	NT

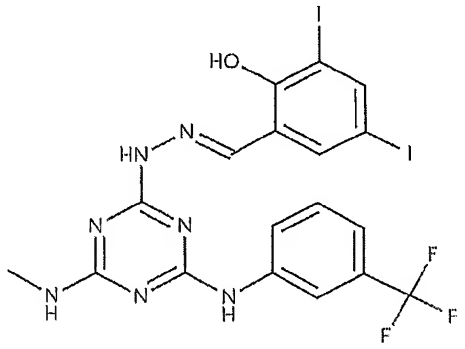
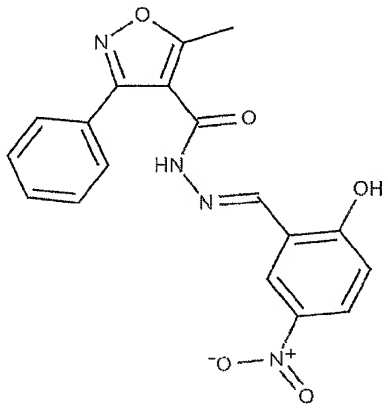
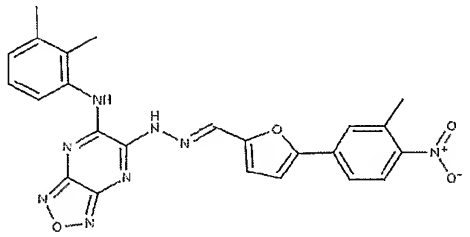
21		+	NT	NT
22		+	NT	NT
23		+	NT	NT

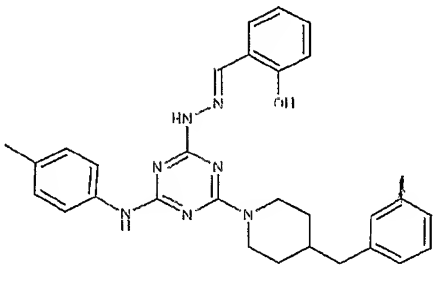
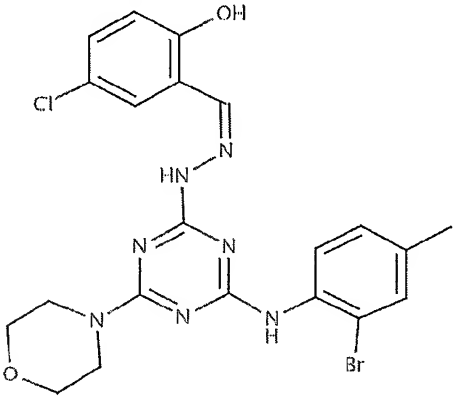
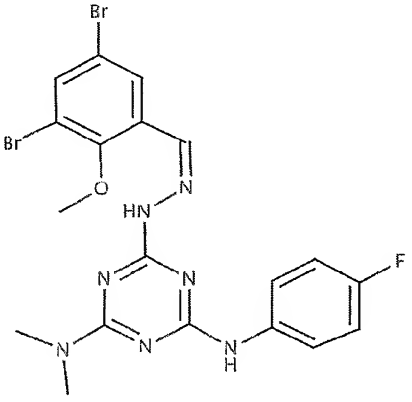
24		+	+	+
25		+	NT	NT
26		+	NT	NT

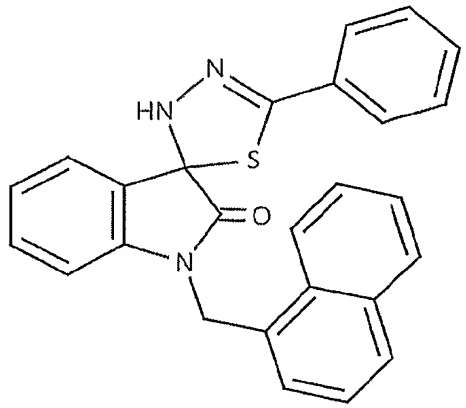
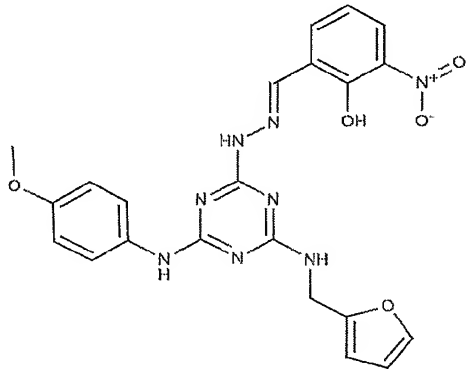
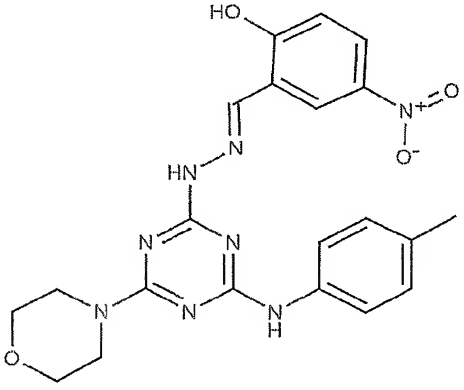
27		+	NT	NT
28		+	–	–
29		+	NT	NT

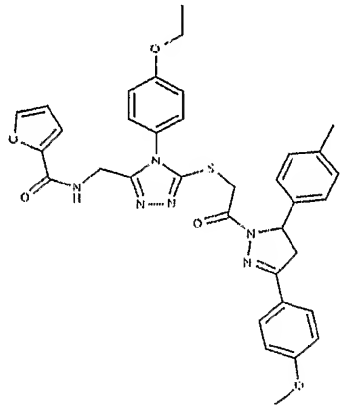
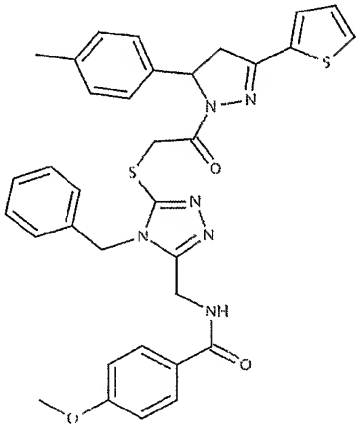
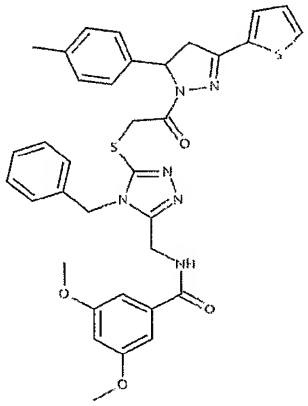
30		+	NT	NT
31		+	NT	NT
32		+	NT	NT

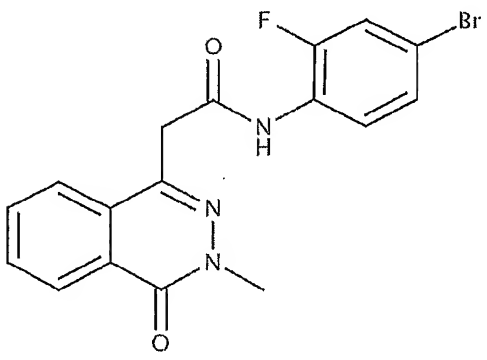
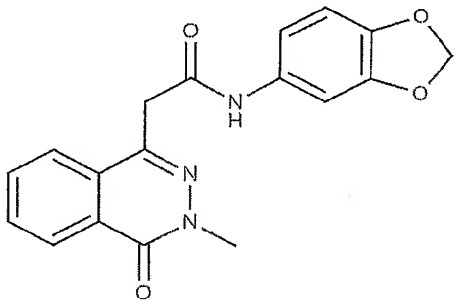
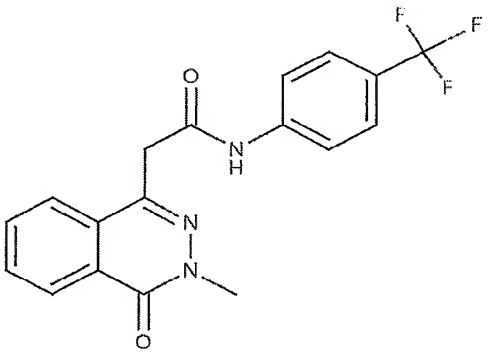
33		+	–	–
34		+	NT	NT
35		+	+	+

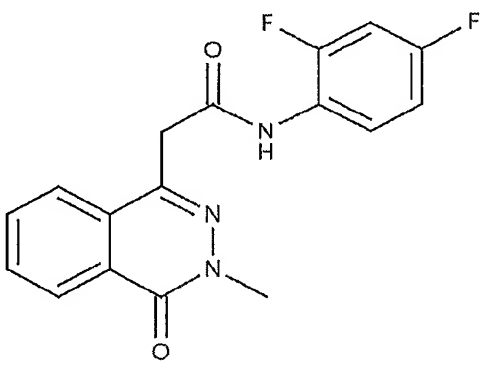
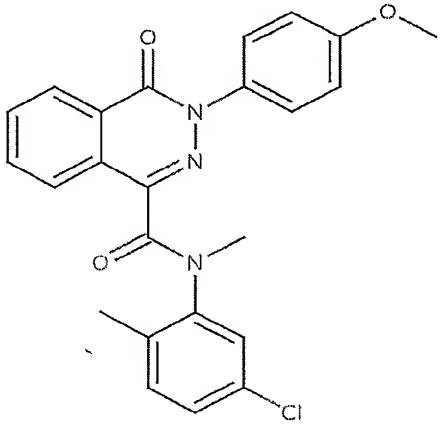
36		+	–	–
37		+	NT	NT
38		+	NT	NT

39		+	NT	NT
40		+	NT	NT
41		+	NT	NT

42		+	NT	NT
43		+	NT	NT
44		+	NT	NT

45		–	NT	NT
46		+	NT	NT
47		–	NT	NT

48		+	NT	NT
49		+	NT	NT
50		+	NT	NT

51		+	NT	NT
52		+	–	–

All units of measurement are in counts/sec luminescent units

"+" means "IC_{50} between 100nM-5uM" for the luciferase reporter assay

"+" means "> or = 2X fold decrease" in ABCA1 transcript for the ABCA1 bDNA

"+" means "> or = 2X fold increase" in HMG CoA Syn transcript for the HMG bDNA

NT means not tested

All results are compared to cells treated with the vehicle control: DMSO

The compounds below have not yet been made, but can generally be made using both literature methods and those methods described above. It is expected that these compounds, when made, will have activity similar to those that have been described in the examples above. The compounds are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages.

Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* 1988, *28*, 31-36.

CCN(N=CC1CC(=O)N(C)C(=C1C#N)C)c2ncc(Br)cc2Cl

CCN(N=CC1CC(=O)NC(=C1C#N)C)c2nnc(Cl)cc2Cl

CCN(N=CC1CCC(=O)NC(=C1C#N)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1CC(=O)Nc2ccccc12)c3ncc(cc3Cl)C(F)(F)F

CN(N=CC1CC(=O)NC2=C1CCCC2)c3ncc(cc3Cl)C(F)(F)F

CN(N=CC1CC(=O)NC(=C1CC=C)C2CC2)c3ncc(cc3Cl)C(F)(F)F

CN(N=CC1CC(=O)Nc2ncccc12)c3ncc(cc3Cl)C(F)(F)F

CN(N=CC1C(=C(C)NC1=O)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1CC(=O)NC2=C1CCCO2)c3ncc(cc3Cl)C(F)(F)F

CN(N=C(C1CC(=O)NC(=C1C#N)C)/c2cccc(c2)S(=O)(=O)C)c3ncc(cc3Cl)C(F)(F)F

CCC1=C(C#N)C(C)(C=NN(C)c2ncc(cc2Cl)C(F)(F)F)C(=O)N1

CN(N=CC1(C)CC(=O)NC(=C1C#N)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1CC(=O)N2CCCC2=C1C#N)c3ncc(cc3Cl)C(F)(F)F

CN(N=CC1C(=O)NC(=C1C#N)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1C(C(=O)NC(=C1C#N)C)C(C)(C)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1C(=C(C)NC(=O)C1(C)C)C#N)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1CC(=O)N(CC2CCC2)C(=C1C#N)C)c3nc4ccccc4nc3Cl

CN(N=CC1CC(=O)N2CCN(C)CC2=C1C#N)c3ncc(cc3Cl)C(F)(F)F

CN(C)CCN1C(=O)CC(C=NN(C)c2nc3ccccc3cc2Cl)C(=C1C)C#N

CN(CC1=C(C)NC(=O)CC1C=NN(C)c2ncc(cc2Cl)C(F)(F)F)C(=O)C

CC(C)Cc1cc(nnc1Cl)C(=N/N(C)c2ncc(cc2Cl)C(F)(F)F)C3CC(=O)NC(=C3C#N)C

CN(N=C1/CCCC12CC(=O)NC(=C2C#N)C)c3ncc(cc3Cl)C(F)(F)F

CN(N=CC1CCC(=O)NC(=C1C)C#N)c2ncc(nc2Cl)C(F)(F)F

CC(C)C1=C(C#N)C(CCC(=O)N1)C=NN(C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1CCCC(=O)NC(=C1C)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=C(/C#N)C1CC(=O)NC(=C1C#N)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=C(/C=O)C1CC(=O)NC(=C1C#N)C)c2ncc(cc2Cl)C(F)(F)F

CC1=C(C#N)C(CC(=O)N1)C=NNc2ncc(Cl)cn2

COCC(C)N1C(=O)CC(C=NNc2ccc3ccccc3c2Cl)C(=C1C)C#N

FC(F)(F)c1cnc(NN=CC2CC(=O)Nc3cccnc23)c(Cl)c1

COc1nc(NC2CCCC2)cc(n1)C(=N/Nc3ncc(cc3Cl)C(F)(F)F)C4CC(=O)NC(=C4C#N)C

CC1CCC(C=NNc2c(Cl)cc(cc2Cl)C(F)(F)F)C(=C(C)NC1=O)C#N

CC1(C)CCC(C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C(=C(NC1=O)C#N)C#N

CCN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1C#N)C)c3ncc(Cl)nc3C

CCC1=C(C#N)C(C)(C=NNc2cscc2C(F)(F)F)C(=O)N1

CCOC(=O)c1nnc(NN=C(C2CC(=O)NC(=C2C#N)C)/c3cc(F)ccn3)nc1Cl

CCN(N=CC1CC(=O)N(CCC2CC2)C(=C1C#N)C)c3nc(Cl)nc(NC)n3

CCN(N=CC1CC(=O)NC(=C1C#N)C)c2nc(Cl)c(n2)C(F)(F)F

CN(N=CC1CCC(C)(C)C(=O)NC(=C1C2CC2)C#N)c3ncc(cc3Cl)C(F)(F)F

CCN(N=CC1CCC(=O)NC(=C1CC#CC)C)c2ncc(Br)cc2Cl

CC1=C(C)C(CCCC(=O)N1)C=NNc2ncc(cc2Cl)C(F)(F)F

CN1CCC(CC1)NN=CC2(C)CC(=O)NC(=C2C#N)C

CCN(N=CC1CC(=O)N(C)C(=C1CC#CC)C)c2ncc(Br)cc2Cl

CCC1=C(CCC#CC)C(C)(C=NN(C)c2nc3ccccc3nc2Cl)C(=O)N1

COCC#CCN(N=CC1CC(=O)N(C(C)COC)C(=C1C#N)C)C2CCN(C)CC2

CC1=C(C2CC2)C(C=NNc3ncc(Cl)cn3)C(C(=O)N1)C(C)(C)C

CN(N=CC1C(=C(C)NC(=O)C1(C)C)C2CC2)c3ncc(nc3Cl)C(F)(F)F

CC1=C(C#N)C(CC(=O)N1)C(=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C#N

CCOC(=O)c1nnc(NN=CC2CC(=O)N(CCC3CC3)C(=C2CCC#CC)C)nc1Cl

CCN(N=CC1(C)CC(=O)NC(=C1CCC#CC)C)c2ncc(cc2Cl)C(F)(F)F

CC#CCCC1=C2CN(C)CCN2C(=O)CC1C=NNC3CCCC3

CCN(N=CC1(C)C(=O)NC(=C1CC#CC)CC)c2ncc(Br)cc2Cl

CCN(N=C(C=O)C1CC(=O)NC(=C1C2CC2)C)c3nc(Cl)c(n3)C(F)(F)F

CCCC1=C(C)NC(=O)CC1C(=NNC2CCN(C)CC2)c3cc(CC(C)C)c(Cl)nn3

CN1CCN2C(=O)CC(C=NN(C(=O)CO)c3csc(n3)C(F)(F)F)C(=C2C1)C4CC4

O=C1CC(C=NNC2CCCC2)C3=C(CCCC3)N1

CC#CCC1=C(C)NC(=O)CC1C(=NNC2CCN(C)CC2)c3cc(CC(C)C)c(Cl)nn3

CCCC1=C(C)NC(=O)CC1C(=NNc2ncc(Cl)cn2)c3cc(F)ccn3

CCN(N=CC1CCC(C)C(=O)NC(=C1CC#CC)C)c2nc(Cl)nc(NC)n2

CCCC1=C2CN(C)CCN2C(=O)CC1C=NN(CC)c3ncc(cc3Cl)C(F)(F)F

CC1=C(C2CC2)C(C)(CC(=O)N1)C=NNc3ccc4ccccc4c3Cl

CC#CCCC1=C(C)C(CCC(=O)N1)C=NN(C)c2ncc(nc2Cl)C(F)(F)F

CCN(N=CC1CC(=O)NC(=C1C#N)C)c2nc(Cl)c(n2)C(F)(F)F

CC#CCCC1=C(C)NC(=O)CC1C=NNc2ncc(Cl)cn2

CC1(C)CCC(C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C(=C(NC1=O)C#N)C#N

CN(N=CC1CC(=O)N2CCN(C)CC2=C1C#N)c3ncc(cc3Cl)C(F)(F)F

CCN(N=C(CCC#CC)C1CC(=O)NC(=C1C#N)C)c2nc(Cl)c(n2)C(F)(F)F

CCN(N=CC1CC(=O)N2CCCC2=C1C#N)c3ncc(Br)cc3Cl

CCN(N=CC1(C)C(=O)NC(=C1C2CC2)CC)c3ncc(cc3Cl)C(F)(F)F

CC1(C)CCC(C=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C(=C(NC1=O)C3CC3)C#N

CCOC(=O)c1nnc(NN=CC2C(=O)NC(=C2C3CC3)C)nc1Cl

CC#CCCC1=C(C)NC(=O)CC1C(=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C#N

CCN(N=CC1CC(=O)N(CCC2CC2)C(=C1C#N)C)c3ncc(Cl)nc3C

CCN(N=CC1CCC(=O)NC(=C1C#N)C)c2nc(Cl)c(n2)C(F)(F)F

CCN(N=CC1C(=O)NC(=C1C#N)C)c2nc(Cl)c(n2)C(F)(F)F

CN1C(=C(C#N)C(CC1=O)C=NNc2cscc2C(F)(F)F)C

CCCC1=C(C)NC(=O)CC1C(=NNC2CCN(C)CC2)c3cc(NC4CCCC4)nc(OC)n3

CCCC1=C(C)NC(=O)CC1C(=NNc2ncc(Cl)cn2)C=O

CC#CCC1=C(C)NC(=O)CC12CCCC2=NN(C3CCOCC3)C(=O)C

CCN(N=CC1C(=C(C)NC(=O)C1(C)C)C#N)c2ncc(Br)cc2Cl

CC#CCC1=C(C)NC(=O)C1C=NNC2CCCC2

CC#CCCC1=C(C#N)C(CCC(C)(C)C(=O)N1)C=NN(C(=O)CO)c2csc(n2)C(F)(F)F

OCC(=O)N(N=CC1CC(=O)Nc2ccccnc12)c3csc(n3)C(F)(F)F

CC#CCC1=C(C)NC(=O)CC1(C)C=NN(C)c2ncc(nc2Cl)C(F)(F)F

CC#CCCC1=C(C)NC(=O)C(C)(C)C1C=NNc2ncc(Cl)cn2

CCCC1=C(C)NC(=O)CC1C(=NN(CC)c2nc(Cl)c(n2)C(F)(F)F)C#N

CC1=C(NC(=O)CCC1C=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C3CC3

CC#CCC1=C2CCCN2C(=O)CC1C=NN(C)c3ncc(cc3Cl)C(F)(F)F

CCN(N=C(C=O)C1CC(=O)NC(=C1C#N)C)c2ncc(Cl)nc2C

CC#CCCC1=C2CCCN2C(=O)CC1C=NN(C)c3ncc(cc3Cl)C(F)(F)F

CC#CCCC1=C(C)N(C)C(=O)CC1C=NN(C)c2ncc(cc2Cl)C(F)(F)F

CC#CCCC1=C(C)NC(=O)CC12CCCC2=NN(C(=O)CO)c3csc(n3)C(F)(F)F

CC1=C(C2CC2)C(CC(=O)N1)C=NNc3ncc(Cl)cn3

CCN(N=CC1CCC(=O)NC(=C1C2CC2)C(C)C)c3ncc(Br)cc3Cl

CC#CCCC1=C(C)N(CCN(C)C)C(=O)CC1C=NNc2ncc(Cl)cn2

CN(N=CC1CCC(=O)NC(=C1C2CC2)C)c3ncc(nc3Cl)C(F)(F)F

CN(N=CC1CC(=O)NC2=C1CCCO2)c3ncc(cc3Cl)C(F)(F)F

CCCC1=C(C)N(Cc2ccccc2)C(=O)CC1C=NNC3CCCC3

CC(C)C1=C(C#N)C(CCC(=O)N1)C=NNc2cscc2C(F)(F)F

CC#CCC1=C(C)NC(=O)CC1C=NNC2CCN(C)CC2

CN(N=CC1CC(=O)N(C)C(=C1C2CC2)C)c3nc4ccccc4nc3Cl

CC#CCCC1=C(NC(=O)CCC1C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C(C)C

CCCC(=NN(CC)c1ncc(cc1Cl)C(F)(F)F)C2CC(=O)NC(=C2C#N)C

CC#CCCC1=C(C)N(Cc2ccccc2)C(=O)CC1C=NN(C3CCOCC3)C(=O)C

CCN(N=C(CC#CC)C1CC(=O)NC(=C1C#N)C)c2nc(Cl)c(n2)C(F)(F)F

CCCC1=C(C)NC(=O)C(C)CCC1C=NNC2CCN(C)CC2

CN(N=CC1CC(=O)Nc2ccccc12)c3ncc(nc3Cl)C(F)(F)F

CN1CCC(CC1)NN=CC2CC(=O)N(CCC3CC3)C(=C2C4CC4)C

CCN(N=C(C#N)C1CC(=O)NC(=C1C2CC2)C)c3ncc(Br)cc3Cl

CCN(N=C(C=O)C1CC(=O)NC(=C1CCC#CC)C)c2ncc(Cl)nc2C

CC#CCC1=C(NC(=O)C(C)(C)CCC1C=NN(C)c2ncc(nc2Cl)C(F)(F)F)C#N

CCN(N=CC1(C)C(=O)NC(=C1C#N)CC)c2ncc(Cl)nc2C

CC1CCC(C=NN(C)c2nc3ccccc3nc2Cl)C(=C(C)NC1=O)C4CC4

CC#CCCC1=C(C)NC(=O)CCC1C=NN(C)c2ncc(cc2Cl)C(F)(F)F

CCOC(=O)c1nnc(NN=CC2CC(=O)N(CC3CCC3)C(=C2C4CC4)C)nc1Cl

CCCC1=C(C)NC(=O)CCC1C=NN(CC)c2nc(Cl)c(n2)C(F)(F)F

CCCC1=C(C)C(CCC(=O)N1)C=NNC2CCCC2

CCN(N=C(C1CC1)C2CC(=O)NC(=C2C#N)C)c3ncc(Cl)nc3C

CCCC1=C(C)N(C)C(=O)CC1C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F

CN(C)CCN1C(=O)CC(C=NNc2ncc(Cl)cn2)C(=C1C)C#N

CN(CC1=C(C)NC(=O)CC1C=NNC2CCCC2)C(=O)C

CC#CCCC1=C(C)N(CC2CCC2)C(=O)CC1C=NNC3CCN(C)CC3

CC#CCC1=C(C#N)C(CCC(C)(C)C(=O)N1)C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F

CCN(N=CC1CCC(=O)NC(=C1C)CC#CC)c2ncc(Cl)nc2C

CC#CCC1=C(NC(=O)CCC1C=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C(C)C

CCN(N=CC1CC(=O)N2CCN(C)CC2=C1CC#CC)c3nc(Cl)c(n3)C(F)(F)F

CCCC1=C(C)NC(=O)CC12CCCC2=NNc3ncc(Cl)cn3

COCC#CCN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1C3CC3)C)C4CCN(C)CC4

CCN(N=CC1CC(=O)N(CCN(C)C)C(=C1CC#CC)C)c2nc(Cl)c(n2)C(F)(F)F

CCOC(=O)c1nnc(NN=C(C#N)C2CC(=O)NC(=C2CC#CC)C)nc1Cl

CCOC(=O)c1nnc(NN=CC2CCC(C)(C)C(=O)NC(=C2CCC#CC)C#N)nc1Cl

CC1=C(NC(=O)CCC1C=NNc2ncc(Cl)cn2)C#N

CC#CCCC1=C(C)NC(=O)CC1C(=NNC2CCCC2)c3cccc(c3)S(=O)(=O)C

COCC#CCN(N=C(C1CC(=O)NC(=C1C#N)C)c2cc(F)ccn2)C3CCN(C)CC3

CCN(N=CC1CC(=O)Nc2ncccc12)c3ncc(Br)cc3Cl

CC#CCCC1=C(C)NC(=O)C(C1C=NN(C2CCOCC2)C(=O)C)C(C)(C)C

CCN(N=CC1CC(=O)N(C(C)COC)C(=C1C2CC2)C)c3nc(Cl)c(n3)C(F)(F)F

CC#CCC1=C(C)NC(=O)C(C1C=NNC2CCCC2)C(C)(C)C

COCC#CCN(N=CC1C(=C(C)NC1=O)C)C2CCN(C)CC2

CCN(N=CC1CC(=O)N2CCCC2=C1C3CC3)c4ncc(Br)cc4Cl

COCC(C)N1C(=O)CC(C=NN(C)c2nc3ccccc3nc2Cl)C(=C1C)CC#CC

CC#CCCC1=C(C)NC(=O)C(C)CCC1C=NN(C)c2ncc(nc2Cl)C(F)(F)F

CCCC1=C(C)NC(=O)C(C)(C)C1C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F

COCC#CCN(N=CC1C(C(=O)NC(=C1C#N)C)C(C)(C)C)C2CCN(C)CC2

CCCC1=C(C)N(CCN(C)C)C(=O)CC1C=NN(C)c2ncc(nc2Cl)C(F)(F)F

CC(C)Cc1cc(nnc1Cl)C(=NN(C2CCOCC2)C(=O)C)C3CC(=O)NC(=C3C4CC4)C

CC#CCC1=C(C)N(CCC2CC2)C(=O)CC1C=NNC3CCCC3

CN(N=CC1CC(=O)N(CC2CCC2)C(=C1C#N)C)c3ncc(cc3Cl)C(F)(F)F

COc1nc(NC2CCCC2)cc(n1)C(=NNC3CCN(C)CC3)C4CC(=O)NC(=C4CC#CC)C

CCCC1=C(C)NC(=O)CC1(C)C=NN(C)c2ncc(cc2Cl)C(F)(F)F

CN(N=C1CCCC12CC(=O)NC(=C2C3CC3)C)c4ncc(nc4Cl)C(F)(F)F

CCCC1=C(NC(=O)CCC1C=NN(CC)c2nc(Cl)nc(NC)n2)C(C)C

CCOC(=O)c1nnc(NN=C(C=O)C2CC(=O)NC(=C2CC#CC)C)nc1Cl

CCCC1=C(NC(=O)C(C)(C)CCC1C=NNc2cscc2C(F)(F)F)C#N

CC1CCC(C=NNc2c(Cl)cc(cc2Cl)C(F)(F)F)C(=C(C)NC1=O)C#N

CC#CCC1=C(C)NC(=O)C(C)(C)C1C=NN(C)c2ncc(nc2Cl)C(F)(F)F

CCCC1=C(C)NC(=O)C(C1C=NNC2CCN(C)CC2)C(C)(C)C

CCCC1=C(C)N(CC2CCC2)C(=O)CC1C=NNC3CCN(C)CC3

CN(C)CCN1C(=C(C2CC2)C(CC1=O)C=NNc3ncc(cc3Cl)C(F)(F)F)C

CCOC(=O)c1nnc(NN=CC2C(=O)NC(=C2CCC#CC)C)nc1Cl

COCC(C)N1C(=O)CC(C=NN(C2CCOCC2)C(=O)C)C(=C1C)CCC#CC

CC1=C(C#N)C2(CCCC2=NNc3cscc3C(F)(F)F)CC(=O)N1

CCCC1=C(CC)NC(=O)C1(C)C=NNC2CCCC2

CCCC1=C(C)N(C(C)COC)C(=O)CC1C=NN(CC)c2nc(Cl)nc(NC)n2

CCCC1=C2CCCN2C(=O)CC1C=NN(C)c3ncc(nc3Cl)C(F)(F)F

CCN(N=C(C1CC(=O)NC(=C1CCC#CC)C)c2cc(F)ccn2)c3nc(Cl)nc(NC)n3

CC1=C(C#N)C(CC(=O)N1)C(=NNc2cscc2C(F)(F)F)c3cccc(c3)S(=O)(=O)C

CC1=C(C2CC2)C(CC(=O)N1)C(=NNc3ccc4ccccc4c3Cl)c5cc(F)ccn5

CC1=C(C#N)C(CC(=O)N1Cc2ccccc2)C=NN(C(=O)CO)c3csc(n3)C(F)(F)F

CCCC1=C(C#N)C(CCC(C)(C)C(=O)N1)C=NN(C)c2ncc(nc2Cl)C(F)(F)F

CN1CCC(CC1)NN=C(C2CC(=O)NC(=C2C3CC3)C)c4cccc(c4)S(=O)(=O)C

CCCC1=C(C)NC(=O)C1C=NN(CC)c2ncc(Br)cc2Cl

CCCC1=C(C)NC(=O)CC1C=NN(CC)c2nc(Cl)nc(NC)n2

CCCC1=C(C)NC(=O)CC1C(=NNC2CCN(C)CC2)c3cccc(c3)S(=O)(=O)C

COc1nc(NC2CCCC2)cc(n1)C(=NNC3CCN(C)CC3)C4CC(=O)NC(=C4C#N)C

CCN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1CC#CC)C)c3nc(Cl)c(n3)C(F)(F)F

CC(C)Cc1cc(nnc1Cl)C(=NNc2ncc(Cl)cn2)C3CC(=O)NC(=C3C#N)C

COc1nc(NC2CCCC2)cc(n1)C(=NNC3CCN(C)CC3)C4CC(=O)NC(=C4C5CC5)C

CC#CCC1=C(C)NC(=O)CC1C(=NN(C)c2ncc(nc2Cl)C(F)(F)F)c3cc(F)ccn3

CCCC1=C(C)N(CCC2CC2)C(=O)CC1C=NNc3nnc(C(=O)OCC)c(Cl)n3

CC#CCC1=C(C)N(CC2CCC2)C(=O)CC1C=NN(C)c3ncc(nc3Cl)C(F)(F)F

CC#CCC1=C(C)NC(=O)CC1C(=NNC2CCN(C)CC2)c3cccc(c3)S(=O)(=O)C

CC#CCCC1=C(C)NC(=O)CC1C(=NNC2CCCC2)c3cc(CC(C)C)c(Cl)nn3

CC#CCC1=C(C)N(C)C(=O)CC1C=NNC2CCCC2

CC1=C(C#N)C(CC(=O)N1)C=NNC2CCCC2

O=C1CC(C=NNC2CCCC2)c3cccnc3N1

CCC1=C(CC#CC)C(C)(C=NNC2CCCC2)C(=O)N1

CC1=C(C2CC2)C(C)(CC(=O)N1)C=NNC3CCCC3

CCCC1=C2CCCN2C(=O)CC1C=NNC3CCCC3

CCCC1=C(C)NC(=O)C(C1C=NNC2CCCC2)C(C)(C)C

CN1CCN2C(=O)CC(C=NNC3CCCC3)C(=C2C1)C#N

CC(C)Cc1cc(nnc1Cl)C(=NNC2CCCC2)C3CC(=O)NC(=C3C4CC4)C

CC1=C(C#N)C2(CCCC2=NNC3CCCC3)CC(=O)N1

CC#CCCC1=C(C)C(CCC(=O)N1)C=NNC2CCCC2

CC#CCCC(=NNC1CCCC1)C2CC(=O)NC(=C2C#N)C

CCCC1=C(C)NC(=O)CC1C(=NNC2CCCC2)C#N

CC#CCCC1=C(C)NC(=O)CC1C(=NNC2CCCC2)C=O

COCC(C)N1C(=O)CC(C=NNC2CCCC2)C(=C1C)C3CC3

O=C1CC(C=NNC2CCCC2)c3ncccc3N1

CC1CCC(C=NNC2CCCC2)C(=C(C)NC1=O)C3CC3

CC1(C)CCC(C=NNC2CCCC2)C(=C(NC1=O)C#N)C3CC3

CC1=C(C2CC2)C(CC(=O)N1Cc3ccccc3)C=NNC4CCCC4

CCCC1=C(C)NC(=O)CC1C(=NNC2CCCC2)c3cc(F)ccn3

CC1=C(C#N)C(CC(=O)N1CCC2CC2)C=NNC3CCCC3

CN1CCC(CC1)NN=CC2CC(=O)N(C)C(=C2C#N)C

CN1CCC(CC1)NN=CC2CC(=O)Nc3ccccc23

CN1CCC(CC1)NN=CC2CC(=O)NC3=C2CCCC3

CN1CCC(CC1)NN=CC2C(=C(C)NC2=O)C

CN1CCC(CC1)NN=CC2CC(=O)NC3=C2CCCO3

CN1CCC(CC1)NN=C(C2CC(=O)NC(=C2C#N)C)c3cccc(c3)S(=O)(=O)C

CCC1=C(C#N)C(C)(C=NNC2CCN(C)CC2)C(=O)N1

CC#CCC1=C(C)NC(=O)CC1(C)C=NNC2CCN(C)CC2

CN1CCC(CC1)NN=CC2CC(=O)N3CCCC3=C2C4CC4

CCCC1=C(C)N(CCN(C)C)C(=O)CC1C=NNC2CCN(C)CC2

CCCC1=C(C)NC(=O)CC12CCCC2=NNC3CCN(C)CC3

CC(C)C1=C(C#N)C(CCC(=O)N1)C=NNC2CCN(C)CC2

CN1CCC(CC1)NN=C(C#N)C2CC(=O)NC(=C2C3CC3)C

CCCC1=C(C)NC(=O)CC1C(=NNC2CCN(C)CC2)C=O

COCC(C)N1C(=O)CC(C=NNC2CCN(C)CC2)C(=C1C)CC#CC

CC#CCCC1=C(NC(=O)C(C)(C)CCC1C=NNC2CCN(C)CC2)C#N

CC#CCCC1=C(C)N(Cc2ccccc2)C(=O)CC1C=NNC3CCN(C)CC3

CN1C(=O)CC(C=NN(C2CCOCC2)C(=O)C)C(=C1C)C#N

CC(=O)N(N=CC1CC(=O)Nc2ccccc12)C3CCOCC3

CC(=O)N(N=CC1CC(=O)Nc2ncccc12)C3CCOCC3

CC(=O)N(N=CC1CC(=O)NC2=C1CCCO2)C3CCOCC3

CC#CCC1=C(C)NC(=O)CC1C(=NN(C2CCOCC2)C(=O)C)c3cccc(c3)S(=O)(=O)C

CCCC1=C(CC)NC(=O)C1(C)C=NN(C2CCOCC2)C(=O)C

CC#CCC1=C(C)NC(=O)CC1(C)C=NN(C2CCOCC2)C(=O)C

CC(=O)N(N=CC1CC(=O)N2CCCC2=C1C3CC3)C4CCOCC4

CC#CCCC1=C(C)NC(=O)C1C=NN(C2CCOCC2)C(=O)C

CC(=O)N(N=CC1C(C(=O)NC(=C1C#N)C)C(C)(C)C)C2CCOCC2

CC(=O)N(N=CC1C(=C(C)NC(=O)C1(C)C)C2CC2)C3CCOCC3

CCCC1=C(C)N(CC2CCC2)C(=O)CC1C=NN(C3CCOCC3)C(=O)C

CC#CCCC1=C2CN(C)CCN2C(=O)CC1C=NN(C3CCOCC3)C(=O)C

CN(C)CCN1C(=O)CC(C=NN(C2CCOCC2)C(=O)C)C(=C1C)C3CC3

CN(CC1=C(C)NC(=O)CC1C=NN(C2CCOCC2)C(=O)C)C(=O)C

CC(C)Cc1cc(nnc1Cl)C(=NN(C2CCOCC2)C(=O)C)C3CC(=O)NC(=C3C#N)C

CC(=O)N(N=C1CCCC12CC(=O)NC(=C2C#N)C)C3CCOCC3

CCCC1=C(NC(=O)CCC1C=NN(C2CCOCC2)C(=O)C)C(C)C

CC#CCC(=NN(C1CCOCC1)C(=O)C)C2CC(=O)NC(=C2C#N)C

CC(=O)N(N=C(C=O)C1CC(=O)NC(=C1C2CC2)C)C3CCOCC3

CC(=O)N(N=CC1CC(=O)Nc2cccnc12)C3CCOCC3

COc1nc(NC2CCCC2)cc(n1)C(=NN(C3CCOCC3)C(=O)C)C4CC(=O)NC(=C4C#N)C

CC#CCC1=C(NC(=O)C(C)(C)CCC1C=NN(C2CCOCC2)C(=O)C)C#N

CC#CCC1=C(C)N(Cc2ccccc2)C(=O)CC1C=NN(C3CCOCC3)C(=O)C

CC(=O)N(N=C(C1CC(=O)NC(=C1C2CC2)C)c3cc(F)ccn3)C4CCOCC4

CC#CCC1=C(C)N(CCC2CC2)C(=O)CC1C=NN(C3CCOCC3)C(=O)C

CCCC1=C(C)NC(=O)CC1C=NN(CC#CCOC)C2CCN(C)CC2

COCC#CCN(N=CC1CC(=O)Nc2ccccc12)C3CCN(C)CC3

COCC#CCN(N=CC1CC(=O)Nc2ncccc12)C3CCN(C)CC3

CCC1=C(C#N)C(C)(C=NN(CC#CCOC)C2CCN(C)CC2)C(=O)N1

COCC#CCN(N=CC1CC(=O)N2CCCC2=C1C#N)C3CCN(C)CC3

CCCC1=C(C)N(CC2CCC2)C(=O)CC1C=NN(CC#CCOC)C3CCN(C)CC3

COCC#CCN(N=CC1CC(=O)N2CCN(C)CC2=C1C3CC3)C4CCN(C)CC4

COCC#CCN(N=C1CCCC12CC(=O)NC(=C2C3CC3)C)C4CCN(C)CC4

COCC#CCN(N=C(C1CC1)C2CC(=O)NC(=C2C#N)C)C3CCN(C)CC3

COCC#CCN(N=CC1CC(=O)Nc2cccnc12)C3CCN(C)CC3

COCC#CCN(N=CC1CCC(C)(C)C(=O)NC(=C1C2CC2)C#N)C3CCN(C)CC3

CC=CCN(N=CC1CC(=O)Nc2ccccc12)c3cccs3

CCCC1=C(C)N(C)C(=O)CC1C=NN(C(=O)CO)c2csc(n2)C(F)(F)F

OCC(=O)N(N=CC1CC(=O)Nc2ncccc12)c3csc(n3)C(F)(F)F

OCC(=O)N(N=CC1CC(=O)NC2=C1CCCO2)c3csc(n3)C(F)(F)F

CCC1=C(CCC#CC)C(C)(C=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C(=O)N1

CC1=C(C#N)C(C)(CC(=O)N1)C=NN(C(=O)CO)c2csc(n2)C(F)(F)F

OCC(=O)N(N=CC1CC(=O)N2CCCC2=C1C3CC3)c4csc(n4)C(F)(F)F

CN1CCN2C(=O)CC(C=NN(C(=O)CO)c3csc(n3)C(F)(F)F)C(=C2C1)C#N

CC1=C(C2CC2)C3(CCCC3=NN(C(=O)CO)c4csc(n4)C(F)(F)F)CC(=O)N1

CCCC1=C(C)C(CCC(=O)N1)C=NN(C(=O)CO)c2csc(n2)C(F)(F)F

CCCC(=NN(C(=O)CO)c1csc(n1)C(F)(F)F)C2CC(=O)NC(=C2C#N)C

CC#CCCC1=C(C)NC(=O)CC1C(=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C=O

CC#CCC1=C(NC(=O)C(C)(C)CCC1C=NN(C(=O)CO)c2csc(n2)C(F)(F)F)C#N

CCCC1=C(C)NC(=O)CC1C(=NN(C(=O)CO)c2csc(n2)C(F)(F)F)c3cc(F)ccn3

CCN(N=CC1CC(=O)N(C)C(=C1C2CC2)C)c3ncc(Br)cc3Cl

CCN(N=CC1CC(=O)NC(=C1C#N)C)c2ncc(Br)cc2Cl

CCN(N=CC1(C)CC(=O)NC(=C1C2CC2)C)c3ncc(Br)cc3Cl

CCN(N=CC1CC(=O)N2CCN(C)CC2=C1CC#CC)c3ncc(Br)cc3Cl

CCCC1=C(C)NC(=O)CC12CCCC2=NN(CC)c3ncc(Br)cc3Cl

CCN(N=CC1CCC(=O)NC(=C1C)CC#CC)c2ncc(Br)cc2Cl

CCN(N=C(C=O)C1CC(=O)NC(=C1CC#CC)C)c2ncc(Br)cc2Cl

CCN(N=CC1CC(=O)N(C)C(=C1CCC#CC)C)c2nnc(Cl)cc2Cl

CCN(N=CC1CC(=O)NC(=C1C2CC2)C)c3nnc(Cl)cc3Cl

CCN(N=CC1CC(=O)Nc2ccccc12)c3nnc(Cl)cc3Cl

CCN(N=CC1(C)C(=O)NC(=C1C#N)CC)c2nnc(Cl)cc2Cl

CCCC1=C(C)NC(=O)CC1(C)C=NN(CC)c2nnc(Cl)cc2Cl

CCN(N=CC1C(C(=O)NC(=C1CC#CC)C)C(C)(C)C)c2nnc(Cl)cc2Cl

CCN(N=CC1CC(=O)N2CCN(C)CC2=C1C#N)c3nnc(Cl)cc3Cl

CCN(N=C1CCCC12CC(=O)NC(=C2CC#CC)C)c3nnc(Cl)cc3Cl

CCCC1=C(C)NC(=O)CC1C(=NN(CC)c2nnc(Cl)cc2Cl)C#N

CCN(N=CC1CC(=O)Nc2cccnc12)c3nnc(Cl)cc3Cl

CCN(N=CC1CCC(C)(C)C(=O)NC(=C1CCC#CC)C#N)c2nnc(Cl)cc2Cl

CCN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1C3CC3)C)c4nnc(Cl)cc4Cl

CCN(N=C(C1CC(=O)NC(=C1C#N)C)c2cc(F)ccn2)c3nnc(Cl)cc3Cl

CCN(N=CC1CC(=O)NC(=C1CCC#CC)C)c2ncc(cc2Cl)C(F)(F)F

CCN(N=CC1CC(=O)N2CCCC2=C1C#N)c3ncc(cc3Cl)C(F)(F)F

CCN(N=CC1CC(=O)Nc2cccnc12)c3ncc(cc3Cl)C(F)(F)F

CCN(N=CC1CCC(C)(C)C(=O)NC(=C1C2CC2)C#N)c3ncc(cc3Cl)C(F)(F)F

CCN(N=C(C1CC(=O)NC(=C1C2CC2)C)c3cc(F)ccn3)c4ncc(cc4Cl)C(F)(F)F

CC#CCC1=C(C)N(C)C(=O)CC1C=NN(C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1CC(=O)Nc2ccccc12)c3ncc(cc3Cl)C(F)(F)F

CCCC1=C(CC)NC(=O)C1(C)C=NN(C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1C(C(=O)NC(=C1C#N)C)C(C)(C)C)c2ncc(cc2Cl)C(F)(F)F

CN(N=CC1CC(=O)N2CCN(C)CC2=C1C3CC3)c4ncc(cc4Cl)C(F)(F)F
CC#CCC1=C(C)NC(=O)CC12CCCC2=NN(C)c3ncc(cc3Cl)C(F)(F)F
CN(N=CC1CCC(=O)NC(=C1C)C2CC2)c3ncc(cc3Cl)C(F)(F)F
CN(N=C(C=O)C1CC(=O)NC(=C1C2CC2)C)c3ncc(cc3Cl)C(F)(F)F
CN(N=CC1CC(=O)N(C)C(=C1C#N)C)c2nc3ccccc3nc2Cl
CC#CCCC1=C(C)NC(=O)CCC1C=NN(C)c2nc3ccccc3nc2Cl
CN(N=CC1CC(=O)Nc2ccccc12)c3nc4ccccc4nc3Cl
CN(N=CC1CC(=O)NC2=C1CCCO2)c3nc4ccccc4nc3Cl
CCC1=C(C#N)C(C)(C=NN(C)c2nc3ccccc3nc2Cl)C(=O)N1
CN(N=CC1CC(=O)N2CCCC2=C1C3CC3)c4nc5ccccc5nc4Cl
CN(N=CC1C(C(=O)NC(=C1C#N)C)C(C)(C)C)c2nc3ccccc3nc2Cl
CC#CCCC1=C2CN(C)CCN2C(=O)CC1C=NN(C)c3nc4ccccc4nc3Cl
CCCC1=C(C)NC(=O)CC12CCCC2=NN(C)c3nc4ccccc4nc3Cl
CN(N=C(C#N)C1CC(=O)NC(=C1C#N)C)c2nc3ccccc3nc2Cl
CN(N=CC1CCC(C)(C)C(=O)NC(=C1C2CC2)C#N)c3nc4ccccc4nc3Cl
CCCC1=C(C)NC(=O)CC1C(=NN(C)c2nc3ccccc3nc2Cl)c4cc(F)ccn4
CC#CCCC1=C(C)N(C)C(=O)CC1C=NN(C)c2nc3ccccc3cc2Cl
CCCC1=C(C)NC(=O)CC1C=NN(C)c2nc3ccccc3cc2Cl
CN(N=CC1CC(=O)Nc2ncccc12)c3nc4ccccc4cc3Cl
CCC1=C(CC#CC)C(C)(C=NN(C)c2nc3ccccc3cc2Cl)C(=O)N1
CN(N=CC1CC(=O)N2CCCC2=C1C#N)c3nc4ccccc4cc3Cl
CN(C)CCN1C(=O)CC(C=NN(C)c2nc3ccccc3cc2Cl)C(=C1C)C4CC4
CN(N=C1CCCC12CC(=O)NC(=C2C#N)C)c3nc4ccccc4cc3Cl
CC#CCC1=C(C)NC(=O)CC1C(=NN(C)c2nc3ccccc3cc2Cl)C#N
CN(N=CC1CC(=O)Nc2cccnc12)c3nc4ccccc4cc3Cl
CN(N=CC1CCC(C)(C)C(=O)NC(=C1C#N)C2CC2)c3nc4ccccc4cc3Cl
CN(N=C(C1CC(=O)NC(=C1C#N)C)c2cc(F)ccn2)c3nc4ccccc4cc3Cl
CCCC1=C(C)N(C)C(=O)CC1C=NN(C)c2ncc(nc2Cl)C(F)(F)F
CN(N=CC1CCC(=O)NC(=C1C#N)C)c2ncc(nc2Cl)C(F)(F)F
CN(N=CC1CC(=O)Nc2ncccc12)c3ncc(nc3Cl)C(F)(F)F
CN(N=CC1CC(=O)NC2=C1CCCO2)c3ncc(nc3Cl)C(F)(F)F
CCC1=C(CC#CC)C(C)(C=NN(C)c2ncc(nc2Cl)C(F)(F)F)C(=O)N1
CCCC1=C(C)NC(=O)C(C)(C)C1C=NN(C)c2ncc(nc2Cl)C(F)(F)F
CN(N=CC1CC(=O)N2CCN(C)CC2=C1C#N)c3ncc(nc3Cl)C(F)(F)F
CC#CCCC1=C(C)NC(=O)CC1C(=NN(C)c2ncc(nc2Cl)C(F)(F)F)C#N
CN(N=CC1CC(=O)Nc2cccnc12)c3ncc(nc3Cl)C(F)(F)F
CN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1C#N)C)c3ncc(nc3Cl)C(F)(F)F
CN(N=C(C1CC(=O)NC(=C1C#N)C)c2cc(F)ccn2)c3ncc(nc3Cl)C(F)(F)F

CCCC1=C(C)N(C)C(=O)CC1C=NNc2ncc(Cl)cn2

CC#CCC1=C(C)NC(=O)CC1C=NNc2ncc(Cl)cn2

Clc1cnc(NN=CC2CC(=O)Nc3ccccc23)nc1

Clc1cnc(NN=CC2CC(=O)Nc3nccccc23)nc1

Clc1cnc(NN=CC2CC(=O)NC3=C2CCCO3)nc1

CC1=C(C2CC2)C(CC(=O)N1)C(=NNc3ncc(Cl)cn3)c4cccc(c4)S(=O)(=O)C

CCC1=C(C#N)C(C)(C=NNc2ncc(Cl)cn2)C(=O)N1

CCCC1=C(C)NC(=O)CC1(C)C=NNc2ncc(Cl)cn2

Clc1cnc(NN=CC2CC(=O)N3CCCC3=C2C#N)nc1

CC#CCC1=C2CN(C)CCN2C(=O)CC1C=NNc3ncc(Cl)cn3

CC1=C(C2CC2)C3(CCCC3=NNc4ncc(Cl)cn4)CC(=O)N1

CC1=C(C#N)C(CC(=O)N1)C(=NNc2ncc(Cl)cn2)C#N

Clc1cnc(NN=CC2CC(=O)Nc3ccccnc23)nc1

CCCC1=C(C)NC(=O)CC1C(=NNc2ncc(Cl)cn2)c3cc(NC4CCCC4)nc(OC)n3

CC#CCC1=C(C#N)C(CCC(C)(C)C(=O)N1)C=NNc2ncc(Cl)cn2

CC1=C(C2CC2)C(CC(=O)N1Cc3ccccc3)C=NNc4ncc(Cl)cn4

CC1=C(C2CC2)C(CC(=O)N1)C(=NNc3ncc(Cl)cn3)c4cc(F)ccn4

CN1C(=O)CC(C=NNc2ccc3ccccc3c2Cl)C(=C1C)C#N

CC#CCCC1=C(C)NC(=O)CCC1C=NNc2ccc3ccccc3c2Cl

Clc1c(NN=CC2CC(=O)Nc3nccccc23)ccc4ccccc14

CC1=C(C)C(C=NNc2ccc3ccccc3c2Cl)C(=O)N1

Clc1c(NN=CC2CC(=O)NC3=C2CCCO3)ccc4ccccc14

CC1=C(C#N)C(CC(=O)N1)C(=NNc2ccc3ccccc3c2Cl)c4cccc(c4)S(=O)(=O)C

CCC1=C(C#N)C(C)(C=NNc2ccc3ccccc3c2Cl)C(=O)N1

CC#CCC1=C2CCCN2C(=O)CC1C=NNc3ccc4ccccc4c3Cl

CN1CCN2C(=O)CC(C=NNc3ccc4ccccc4c3Cl)C(=C2C1)C5CC5

CN(CC1=C(C)NC(=O)CC1C=NNc2ccc3ccccc3c2Cl)C(=O)C

CC1=C(C#N)C2(CCCC2=NNc3ccc4ccccc4c3Cl)CC(=O)N1

CC1=C(C2CC2)C(CC(=O)N1)C(=NNc3ccc4ccccc4c3Cl)C#N

CCCC1=C(C)NC(=O)CC1C(=NNc2ccc3ccccc3c2Cl)C=O

CC1=C(C#N)C(CC(=O)N1)C(=NNc2ccc3ccccc3c2Cl)c4cc(F)ccn4

CN1C(=O)CC(C=NNc2ncc(cc2Cl)C(F)(F)F)C(=C1C)C3CC3

CC1=C(C#N)C(CC(=O)N1)C=NNc2ncc(cc2Cl)C(F)(F)F

FC(F)(F)c1cnc(NN=CC2CC(=O)Nc3nccccc23)c(Cl)c1

FC(F)(F)c1cnc(NN=CC2CC(=O)NC3=C2CCCO3)c(Cl)c1

CCC1=C(CC#CC)C(C)(C=NNc2ncc(cc2Cl)C(F)(F)F)C(=O)N1

CC#CCC1=C2CCCN2C(=O)CC1C=NNc3ncc(cc3Cl)C(F)(F)F

CN1CCN2C(=O)CC(C=NNc3ncc(cc3Cl)C(F)(F)F)C(=C2C1)C#N

CCCC1=C(C)NC(=O)CC12CCCC2=NNc3ncc(cc3Cl)C(F)(F)F

CC#CCC1=C(C)NC(=O)CC1C(=NNc2ncc(cc2Cl)C(F)(F)F)C=O

CC#CCCC1=C(NC(=O)C(C)(C)CCC1C=NNc2ncc(cc2Cl)C(F)(F)F)C#N

CCCC1=C(C)NC(=O)CC1C(=NNc2ncc(cc2Cl)C(F)(F)F)c3cc(F)ccn3

CC1=C(C2CC2)C(CCC(=O)N1)C=NNc3c(Cl)cc(cc3Cl)C(F)(F)F

FC(F)(F)c1cc(Cl)c(NN=CC2CC(=O)NC3=C2CCCO3)c(Cl)c1

CC1=C(C#N)C(C)(CC(=O)N1)C=NNc2c(Cl)cc(cc2Cl)C(F)(F)F

FC(F)(F)c1cc(Cl)c(NN=CC2CC(=O)N3CCCC3=C2C#N)c(Cl)c1

CC#CCCC1=C(C)NC(=O)CC1C(=NNc2c(Cl)cc(cc2Cl)C(F)(F)F)C#N

FC(F)(F)c1cc(Cl)c(NN=CC2CC(=O)Nc3ccccnc23)c(Cl)c1

CC1(C)CCC(C=NNc2c(Cl)cc(cc2Cl)C(F)(F)F)C(=C(NC1=O)C#N)C#N

CC#CCCC1=C(C)N(C)C(=O)CC1C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F

CC1=C(C#N)C(CC(=O)N1)C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F

FC(F)(F)c1nc(Cl)c(NN=CC2CC(=O)Nc3ccccc23)c(Cl)n1

FC(F)(F)c1nc(Cl)c(NN=CC2CC(=O)NC3=C2CCCO3)c(Cl)n1

CCC1=C(CCC#CC)C(C)(C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C(=O)N1

CC1=C(C2CC2)C(C)(CC(=O)N1)C=NNc3c(Cl)nc(nc3Cl)C(F)(F)F

FC(F)(F)c1nc(Cl)c(NN=CC2CC(=O)N3CCCC3=C2C4CC4)c(Cl)n1

CN1CCN2C(=O)CC(C=NNc3c(Cl)nc(nc3Cl)C(F)(F)F)C(=C2C1)C#N

CCCC1=C(C)NC(=O)CC12CCCC2=NNc3c(Cl)nc(nc3Cl)C(F)(F)F

CCCC1=C(NC(=O)CCC1C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C(C)C

CC#CCCC1=C(C)NC(=O)CC1C(=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C#N

FC(F)(F)c1nc(Cl)c(NN=CC2CC(=O)Nc3ccccnc23)c(Cl)n1

CC#CCC1=C(NC(=O)C(C)(C)CCC1C=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C#N

CC1=C(C#N)C(CC(=O)N1Cc2ccccc2)C=NNc3c(Cl)nc(nc3Cl)C(F)(F)F

CCN(N=CC1CC(=O)N(C)C(=C1C#N)C)c2ncc(Cl)nc2C

CCCC1=C(C)NC(=O)CCC1C=NN(CC)c2ncc(Cl)nc2C

CCN(N=CC1CC(=O)Nc2ccccc12)c3ncc(Cl)nc3C

CCN(N=CC1CC(=O)NC2=C1CCCO2)c3ncc(Cl)nc3C

CCN(N=C(C1CC(=O)NC(=C1C#N)C)c2cccc(c2)S(=O)(=O)C)c3ncc(Cl)nc3C

CCN(N=CC1(C)CC(=O)NC(=C1CC#CC)C)c2ncc(Cl)nc2C

CCN(N=CC1CC(=O)N2CCCC2=C1CC#CC)c3ncc(Cl)nc3C

CCN(N=CC1C(C(=O)NC(=C1C#N)C)C(C)(C)C)c2ncc(Cl)nc2C

CCCC1=C2CN(C)CCN2C(=O)CC1C=NN(CC)c3ncc(Cl)nc3C

CCN(N=C(CCC#CC)C1CC(=O)NC(=C1C#N)C)c2ncc(Cl)nc2C

CCN(N=C(C=O)C1CC(=O)NC(=C1C2CC2)C)c3ncc(Cl)nc3C

CCN(N=CC1CCC(C)(C)C(=O)NC(=C1CC#CC)C#N)c2ncc(Cl)nc2C

CCN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1C3CC3)C)c4ncc(Cl)nc4C

CCN(N=C(C1CC(=O)NC(=C1CCC#CC)C)c2cc(F)ccn2)c3ncc(Cl)nc3C

CCCC1=C(C)NC(=O)CC1C=NNc2cscc2C(F)(F)F

FC(F)(F)c1cscc1NN=CC2CC(=O)Nc3ccccc23

CCC1=C(C#N)C(C)(C=NNc2cscc2C(F)(F)F)C(=O)N1

CC#CCC1=C(C)NC(=O)CC1(C)C=NNc2cscc2C(F)(F)F

CC#CCCC1=C2CCCN2C(=O)CC1C=NNc3cscc3C(F)(F)F

CN1CCN2C(=O)CC(C=NNc3cscc3C(F)(F)F)C(=C2C1)C4CC4

CC1=C(C2CC2)C3(CCCC3=NNc4cscc4C(F)(F)F)CC(=O)N1

CC#CCCC(=NNc1cscc1C(F)(F)F)C2CC(=O)NC(=C2C#N)C

CC1=C(C2CC2)C(CC(=O)N1Cc3ccccc3)C=NNc4cscc4C(F)(F)F

CC#CCC1=C(C)NC(=O)CC1C(=NNc2cscc2C(F)(F)F)c3cc(F)ccn3

CCOC(=O)c1nnc(NN=CC2CC(=O)N(C)C(=C2C3CC3)C)nc1Cl

CCOC(=O)c1nnc(NN=CC2CC(=O)NC(=C2C#N)C)nc1Cl

CCOC(=O)c1nnc(NN=CC2CC(=O)Nc3ncccc23)nc1Cl

CCOC(=O)c1nnc(NN=CC2CC(=O)NC3=C2CCCO3)nc1Cl

CCOC(=O)c1nnc(NN=CC2(C)C(=O)NC(=C2CCC#CC)CC)nc1Cl

CCOC(=O)c1nnc(NN=CC2CC(=O)N3CCN(C)CC3=C2C#N)nc1Cl

CCCC1=C(C)NC(=O)CC12CCCC2=NNc3nnc(C(=O)OCC)c(Cl)n3

CCOC(=O)c1nnc(NN=CC2CC(=O)N(Cc3ccccc3)C(=C2CCC#CC)C)nc1Cl

CCOC(=O)c1nnc(NN=C(C2CC(=O)NC(=C2CCC#CC)C)c3cc(F)ccn3)nc1Cl

CCCC1=C(C)N(C)C(=O)CC1C=NN(CC)c2nc(Cl)nc(NC)n2

CCN(N=CC1CC(=O)NC(=C1C#N)C)c2nc(Cl)nc(NC)n2

CCN(N=CC1CC(=O)Nc2ccccc12)c3nc(Cl)nc(NC)n3

CCN(N=CC1(C)C(=O)NC(=C1CCC#CC)CC)c2nc(Cl)nc(NC)n2

CCN(N=CC1C(C(=O)NC(=C1C2CC2)C)C(C)(C)C)c3nc(Cl)nc(NC)n3

CCN(N=CC1CC(=O)N2CCN(C)CC2=C1C#N)c3nc(Cl)nc(NC)n3

CCCC1=C(C)NC(=O)CC12CCCC2=NN(CC)c3nc(Cl)nc(NC)n3

CCN(N=C(C=O)C1CC(=O)NC(=C1CC#CC)C)c2nc(Cl)nc(NC)n2

CCN(N=CC1CCC(C)(C)C(=O)NC(=C1CC#CC)C#N)c2nc(Cl)nc(NC)n2

CCN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1C#N)C)c3nc(Cl)nc(NC)n3

CCCC1=C(C)NC(=O)CC1C(=NN(CC)c2nc(Cl)nc(NC)n2)c3cc(F)ccn3

CCN(N=CC1CC(=O)N(C)C(=C1CCC#CC)C)c2nc(Cl)c(n2)C(F)(F)F

CCCC1=C(C)NC(=O)CC1C=NN(CC)c2nc(Cl)c(n2)C(F)(F)F

CCN(N=CC1CC(=O)Nc2ccccc12)c3nc(Cl)c(n3)C(F)(F)F

CCN(N=CC1(C)C(=O)NC(=C1C#N)CC)c2nc(Cl)c(n2)C(F)(F)F

CCN(N=CC1(C)CC(=O)NC(=C1CC#CC)C)c2nc(Cl)c(n2)C(F)(F)F

CCN(N=CC1CC(=O)N2CCCC2=C1C#N)c3nc(Cl)c(n3)C(F)(F)F

CCN(N=CC1C(C(=O)NC(=C1C#N)C)C(C)(C)C)c2nc(Cl)c(n2)C(F)(F)F

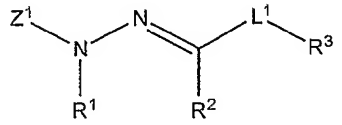
CCN(N=CC1CC(=O)N2CCN(C)CC2=C1C3CC3)c4nc(Cl)c(n4)C(F)(F)F
CCCC1=C(C)NC(=O)CC12CCCC2=NN(CC)c3nc(Cl)c(n3)C(F)(F)F
CCN(N=CC1CCC(C)(C)C(=O)NC(=C1CCC#CC)C#N)c2nc(Cl)c(n2)C(F)(F)F
CCN(N=CC1CC(=O)N(Cc2ccccc2)C(=C1C3CC3)C)c4nc(Cl)c(n4)C(F)(F)F
CCN(N=C(C1CC(=O)NC(=C1CC#CC)C)c2cc(F)ccn2)c3nc(Cl)c(n3)C(F)(F)F
CN1CCC(CC1)NN=CC2CCC(C)(C)C(=O)NC(=C2C#N)C3CC3
CC1=C(C2CC2)C(CC(=O)N1)C(=NNC3CCCC3)c4cc(F)ccn4
CC1=C(C#N)C(CC(=O)N1)C(=NNc2c(Cl)nc(nc2Cl)C(F)(F)F)C=O
CC#CCC1=C(C)NC(=O)CC1C=NNc2ccc3ccccc3c2Cl
CCCC1=C(C)NC(=O)C(C)(C)C1C=NNc2cscc2C(F)(F)F
CC#CCCC1=C(C)NC(=O)CC12CCCC2=NN(C)c3ncc(nc3Cl)C(F)(F)F
CCN(N=C1CCCC12CC(=O)NC(=C2CC#CC)C)c3nc(Cl)nc(NC)n3
CCCC1=C(C#N)C(CCC(C)(C)C(=O)N1)C=NNc2nnc(C(=O)OCC)c(Cl)n2
CCCC1=C(C)NC(=O)CC1C(=NN(CC)c2nnc(Cl)cc2Cl)c3cc(F)ccn3
CC(C)C1=C(C#N)C(CCC(=O)N1)C=NNc2c(Cl)cc(cc2Cl)C(F)(F)F
COCC#CCN(N=CC1CC(=O)N2CCN(C)CC2=C1C#N)C3CCN(C)CC3
CCC1=C(C#N)C(C)(C=NNc2ncc(cc2Cl)C(F)(F)F)C(=O)N1
CCN(N=CC1CC(=O)NC(=C1CN(C)C(=O)C)C)c2ncc(cc2Cl)C(F)(F)F
CCCC1=C(C)NC(=O)CC12CCCC2=NN(C3CCOCC3)C(=O)C
CC1=C(C)C(C=NNc2ncc(Cl)cn2)C(=O)N1
CCN(N=C(CC#CC)C1CC(=O)NC(=C1C#N)C)c2ncc(Cl)nc2C
CC(C)C1=C(C#N)C(CCC(=O)N1)C=NN(C)c2nc3ccccc3cc2Cl
CC#CCC1=C(C)NC(=O)CC1C(=NN(C)c2ncc(cc2Cl)C(F)(F)F)C#N
CCN(N=C(CCC#CC)C1CC(=O)NC(=C1C#N)C)c2ncc(Br)cc2Cl
CC=CCN(N=CC1CC(=O)Nc2cccnc12)c3cccs3

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A method of inhibiting NPC1L1 comprising the administration of a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

Z^1 is selected from the group consisting of Y^1, Y^2, and Y^3;

Y^1 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, perhaloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

Y^2 is selected from the group consisting of R^4–L^2–C(O)– and R^4–L^2–C(S)–;

Y^3 is $C(R^5)(R^6)(R^7)$;

L^1 and L^2 are independently selected from the group consisting of a bond and optionally substituted lower alkyl;

R^1 is selected from the group consisting of hydrogen, lower acyl, lower alkyl; lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^2 is selected from the group consisting of hydrogen, -S-, cyano, formyl, lower acyl, lower alkyl, heteroaryl, and aryl, any of which may be optionally substituted; or R^1 and R^2, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted heteroaryl moiety;

R^3 is selected from the group consisting of lower acyl, lower alkenyl, lower alkenylsulfonyl, lower alkyl, lower alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, heteroaryl, heteroarylsulfonyl, heterocycloalkyl, and heterocycloalkylsulfonyl, any of which may be optionally substituted; or R^2 and R^3, together with the atoms to which they are attached, may be joined to form an optionally substituted cycloalkyl or optionally substituted heterocycloalkyl moiety;

R^4 is selected from the group consisting of hydrogen, aryl, arylalkoxy, arylalkylamino, arylalkylthio, arylamino, aryloxy, arylthio, heteroarylalkoxy, heteroarylalkylamino, heteroarylalkylthio, heteroaryl, heteroarylthio, heterocycloalkyl, and heterocycloalkylthio, any

of which may be optionally substituted; or R^2 and R^4, taken together with the atoms to which they are attached, may form an optionally substituted heteroaryl or optionally substituted heterocycloalkyl moiety; and

R^5, R^6, and R^7 are independently selected from the group consisting of hydrogen, -S-, amido, aryl, lower alkyl, and heteroaryl, any of which may be optionally substituted.

2. The method as recited in Claim 1, wherein:

Y^1 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

Y^2 is R^4–L^2–C(O)– ;

R^1 is selected from the group consisting of hydrogen and optionally substituted alkyl;

R^2 is hydrogen or is selected from the group consisting of optionally substituted lower alkyl, optionally substituted heteroaryl, and optionally substituted aryl;

R^3 is selected from the group consisting of lower acyl, aryl, arylsulfonyl, heteroaryl, heteroarylsulfonyl, heterocycloalkyl, and heterocycloalkylsulfonyl, any of which may be optionally substituted; and

R^4 is selected from the group consisting of aryl, arylalkoxy, arylalkylamino, arylamino, aryloxy, arylthio, heteroarylalkoxy, heteroaryl, and heteroarylthio, any of which may be optionally substituted; or R^2 and R^4, taken together with the atoms to which they are attached, may form an optionally substituted heteroaryl or optionally substituted heterocycloalkyl moiety.

3. The method as recited in Claim 2, wherein:

Z^1 is Y^1;

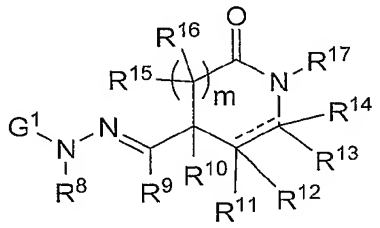
L^1 is a bond;

R^1 is optionally substituted alkyl;

R^2 is hydrogen and optionally substituted lower alkyl; and

R^3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

4. The method as recited in Claim 1 comprising the administration of a compound of structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

G^1 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, perhaloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^8 is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^9 is selected from the group consisting of hydrogen, cyano, formyl, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower perhaloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^8 and R^9, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{10} is selected from the group consisting hydrogen, lower alkyl, lower alkenyl, and lower alkynyl, any of which may be optionally substituted; or R^9 and R^{10}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{11} and R^{14} are independently selected from the group consisting of hydrogen, cyano, lower alkyl, lower alkenyl, lower alkynyl, and lower cycloalkyl, any of which may be optionally substituted; or R^{11} and R^{14}, together with the atoms to which they are attached, may be joined to form an aryl, heteroaryl, heterocycloalkyl or cycloalkyl moiety, any of which may be optionally substituted;

R^{12} and R^{13} are independently selected from the group consisting of null, hydrogen and optionally substituted lower alkyl;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl; or R^{15} and R^{16}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

m is an integer from 0 to 3; and

R^{17} is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower aminoalkyl, lower cycloalkyl, lower cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{14} and R^{17}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl moiety.

5. The method as recited in Claim 4, wherein:

G^1 is selected from optionally substituted aryl and optionally substituted heteroaryl;

R^8 is selected from the group consisting of hydrogen, lower alkyl, aryl and heteroaryl, any of which may be optionally substituted;

R^9 is selected from the group consisting of hydrogen, cyano, formyl, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted; or R^8 and R^9, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{10} is selected from the group consisting of hydrogen and optionally substituted lower alkyl; or R^9 and R^{10}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{11} and R^{14} are independently selected from the group consisting of hydrogen, cyano and optionally substituted lower alkyl; or R^{11} and R^{14}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

m is an integer from 1 to 2; and

R^{17} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; or R^{14} and R^{17}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted heterocycloalkyl moiety.

6. The method as recited in Claim 5, wherein:

G^1 is optionally substituted heteroaryl;

R^8 is optionally substituted lower alkyl;

R^9 is hydrogen;

R^{10} is hydrogen;

R^{11} and R^{14} are independently selected from the groups consisting of cyano and optionally substituted lower alkyl;

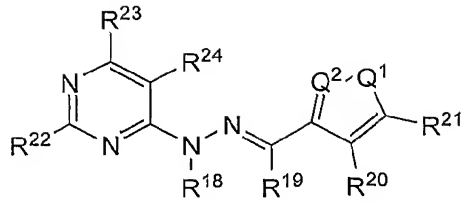
R^{12} and $R^{13}$are null;

R^{15} and R^{16} are hydrogen;

m is 1; and

R^{17} is hydrogen.

7. The method as recited in Claim 1 comprising the administration of a compound of structural Formula III:



(III)

or a salt, ester, or prodrug thereof, wherein:

R^{18} is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower perhaloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{20}, R^{21}, R^{23} and R^{24} are independently selected from the group consisting of hydrogen, amino, hydroxy, carbamoyl, carboxy, halogen, cyano, nitro, lower acyl, lower acylamino, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkylthioalkyl, lower alkenyl, lower alkynyl, lower aminoalkyl, lower aminocarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylalkynyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, lower haloalkoxy, lower haloalkyl, lower perhaloalkyl, lower heteroalkyl, lower perhaloalkoxy, trihalomethanesulfonamido, trihalomethanesulfonyl, trihalomethoxy, trisubstituted silyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl, any of which may be optionally substituted; or R^{20} and R^{21}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted; or R^{23} and R^{24}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted;

R^{22} is selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, lower haloalkoxy, lower perhaloalkyl, lower perhaloalkoxy, and trihalomethoxy;

Q^1 is selected from the group consisting of $N(R^{25})$, O, and S;

Q^2 is selected from the group consisting of $N(R^{26})$, $C(R^{27})$, O, and S; and

R^{25}, R^{26} and R^{27} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, and lower perhaloalkyl.

8. The method as recited in Claim 7 wherein:

R^{18} is selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{20}, R^{21}, R^{23} and R^{24} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, aryl, arylalkyl, lower perhaloalkyl, lower perhaloalkoxy, heterocycloalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; or either pair of R^{20} and R^{21} or R^{23} and R^{24}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted;

R^{22} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

Q^1 is selected from the group consisting of $N(R^{25})$, O, and S;

Q^2 is $C(R^{27})$; and

R^{25} and R^{27} are independently selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl.

9. The method as recited in Claim 8 wherein:

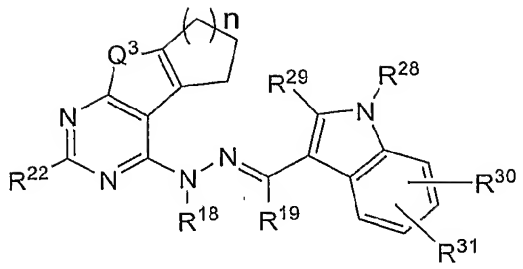
R^{18} is selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R^{19} is selected from the group consisting of hydrogen and optionally substituted alkyl; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{20} and R^{21}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted; or R^{23} and R^{24}, together with the atoms to which they are attached, may be joined to form an aryl, cycloalkyl, heterocycloalkyl or heteroaryl ring, any of which may be optionally substituted; and

R^{22} is selected from the group consisting of hydrogen and optionally substituted lower alkyl.

10. The method as recited in Claim 9, wherein the compound has the structural Formula IV:



(IV)

or a salt, ester, or prodrug thereof, wherein:

R^{18} is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, arylalkenyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocycloalkyl, and perhaloalkyl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower perhaloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{22} is selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, lower haloalkoxy, lower perhaloalkyl, lower perhaloalkoxy, and trihalomethoxy;

Q^3 is selected from the group consisting of $N(R^{28})$, O, and S;

n is an integer from 1 to 4;

$R^{28}$and R^{29} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, and lower perhaloalkyl; and

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, amino, hydroxy, carbamoyl, carboxy, halogen, cyano, nitro, lower acyl, lower acylamino, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkylthioalkyl, lower alkenyl, lower alkynyl, lower aminoalkyl, lower aminocarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylalkynyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, lower haloalkoxy, lower haloalkyl, lower perhaloalkyl, lower heteroalkyl, lower perhaloalkoxy, trihalomethanesulfonamido,

trihalomethanesulfonyl, trihalomethoxy, trisubstituted silyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl, any of which may be optionally substituted.

11. The method as recited in Claim 10 wherein:

R^{18} is selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted;

R^{19} is selected from the group consisting of hydrogen, cyano, formyl, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted; or R^{18} and R^{19}, together with the atoms to which they are attached, may be joined to form a heterocycloalkyl or heteroaryl moiety, either of which may be optionally substituted;

R^{22} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

R^{28} and R^{29} are independently selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, and lower alkylsulfonyl; and

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, cyano, lower alkoxy, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower perhaloalkyl, and lower perhaloalkoxy, any of which may be optionally substituted.

12. The method as recited in Claim 11, wherein:

R^{18} is selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R^{19} is selected from the group consisting of hydrogen and optionally substituted alkyl;

R^{22} is selected from the group consisting of hydrogen and optionally substituted lower alkyl;

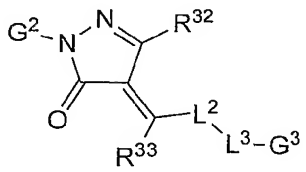
Q^3 is S;

n is the integer 2;

R^{28} and R^{29} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl; and

R^{30} and R^{31} are independently hydrogen and optionally substituted lower alkyl.

13. The method as recited in Claim 1 comprising the administration of a compound of structural Formula V:



(V)

or a salt, ester, or prodrug thereof, wherein:

G^2 and G^3 are independently selected from the group consisting of aryl, lower cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may be optionally substituted;

R^{32} is selected from the group consisting of hydrogen, carbamoyl, cyano, lower acyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkylsulfonyl, lower alkylthio, lower alkenyl, lower alkynyl, lower aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, carboxy, lower perhaloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl, any of which may be optionally substituted;

R^{33} is selected from the group consisting of hydrogen, lower acyl, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower alkanoyl, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, lower alkenyl, lower alkynyl, lower aminocarbonylalkyl, lower perhaloalkyl, any of which may be optionally substituted;

L^2 is selected from the group consisting of $N(R^{34})$, O, and S;

L^3 is selected from the group consisting of a bond, $-NHC(=O)-$, $-C(R^{35})(R^{36})-$; and

R^{34}, R^{35} and R^{36} are independently selected from the group consisting of hydrogen and optionally substituted alkyl.

14. The method as recited in Claim 13 wherein:

G^2 and G^3 are independently selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted;

R^{32} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

R^{33} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted;

L^2 is $N(R^{34})$; and

R^{34}, R^{35} and R^{36} are hydrogen.

15. The method as recited in Claim 14 wherein:

G^2 and G^3 are independently selected from optionally substituted aryl;

R^{32} is optionally substituted lower alkyl;

L^3 is a bond; and

R^{33} is hydrogen.

16. The method as recited in Claim 1 wherein said compound is selected from the group consisting of Examples 1 to 52.

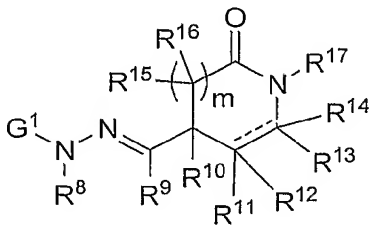
17. The method as recited in Claim 1 where said method is inhibiting NPC1L1 activity in a patient in need thereof comprising the administration of a therapeutically effective amount of said compound.

18. The method as recited in Claim 17 wherein said method has the effect of lowering of cholesterol absorption in a patient in need thereof.

19. The method as recited in Claim 17 further comprising the administration of a statin.

20. The method as recited in Claim 19 wherein said statin is selected from the group consisting of lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin.

21. A compound of structural Formula II:



(II)

or a salt, ester, or prodrug thereof, wherein:

G^1 is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^8 is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, aryl, and heteroaryl, any of which may be optionally substituted;

R^9 is selected from the group consisting of cyano, formyl, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower perhaloalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, any of which may be optionally substituted;

R^{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, and lower alkynyl, any of which may be optionally substituted; or R^9 and R^{10}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{11} and R^{14} are independently selected from the group consisting of hydrogen, cyano, lower alkyl, lower alkenyl, lower alkynyl, and lower cycloalkyl, any of which may be optionally substituted; or R^{11} and R^{14}, together with the atoms to which they are attached, may be joined to form an aryl, heteroaryl, heterocycloalkyl or cycloalkyl moiety, any of which may be optionally substituted;

R^{12} and R^{13} are independently selected from the group consisting of null, hydrogen and optionally substituted lower alkyl;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

m is an integer from 0 to 3; and

R^{17} is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower aminoalkyl, lower cycloalkyl, lower cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, and heterocycloalkyl, any of which may be optionally substituted; or R^{14} and R^{17}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety.

22. The compound as recited in Claim 21, wherein:

G^1 is selected from optionally substituted aryl and optionally substituted heteroaryl;

R^8 is selected from hydrogen and optionally substituted lower alkyl;

R^9 is selected from the group consisting of cyano, formyl, lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted;

R^{10} is selected from the group consisting of hydrogen and optionally substituted lower alkyl; or R^9 and R^{10}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{11} and R^{14} are independently selected from the group consisting of hydrogen, cyano, and optionally substituted lower alkyl; or R^{11} and R^{14}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted cycloalkyl moiety;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

m is an integer from 1 to 2; and

R^{17} is selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; or R^{14} and R^{17}, together with the atoms to which they are attached, may be joined to form an optionally substituted heterocycloalkyl or optionally substituted heterocycloalkyl moiety.

23. A compound as recited in Claim 22, wherein:

G^1 is optionally substituted heteroaryl;

R^8 is optionally substituted lower alkyl;

R^9 is selected from the group consisting of lower alkyl, aryl, and heteroaryl, any of which may be optionally substituted;

R^{10} is hydrogen;

R^{11} and R^{14} are independently selected from the groups consisting of cyano and optionally substituted lower alkyl;

R^{12} and $R^{13}$are null;

R^{15} and R^{16} are hydrogen;

m is 1; and

R^{17} is hydrogen.

24. A pharmaceutical composition comprising a compound as recited in Claim 21 together with a pharmaceutically acceptable carrier.
25. The pharmaceutical composition as recited in Claim 24 further comprising a statin.
26. The pharmaceutical composition as recited in Claim 25 wherein said statin is selected from the group consisting of lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin.
27. The use of the compound as recited in Claim 1 for the manufacture of a medicament for lowering of cholesterol absorption in a patient in need thereof.